

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 401/04, A61K 31/44		A1	(11) International Publication Number: WO 97/16442 (43) International Publication Date: 9 May 1997 (09.05.97)
(21) International Application Number: PCT/US96/18539 (22) International Filing Date: 30 October 1996 (30.10.96)		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, AR IPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(30) Priority Data: 60/007,100 31 October 1995 (31.10.95) US 9605158.6 12 March 1996 (12.03.96) GB 60/015,565 18 April 1996 (18.04.96) US 9612062.1 10 June 1996 (10.06.96) GB		Published <i>With international search report.</i>	
(71) Applicant (<i>for all designated States except US</i>): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).			
(72) Inventors; and (75) Inventors/Applicants (<i>for US only</i>): de LASZLO, Stephen, E. [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). CHANG, Linda, L. [CA/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). KIM, Dooseop [KR/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MANTLO, Nathan, B. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).			
(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).			

(54) Title: SUBSTITUTED PYRIDYL PYRROLES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF USE

(57) Abstract

The present invention addresses substituted pyridyl pyrroles, as well as compositions containing such compounds and methods of treatment. The compounds in the present invention are glucagon antagonists and inhibitors of the biosynthesis and action of TNF- α and IL1. The compounds block the action of glucagon at its receptors and thereby decrease the levels of plasma glucose. The instant pyrroles are also inhibitors of TNF- α and IL1 and may be used as antidiabetic agents as well as other cytokine mediated diseases. Cytokine mediated diseases refer to diseases or conditions in which excessive or unregulated production of one or more cytokines occurs. Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are cytokines produced by a variety of cells, which are involved in immunoregulation and other physiological conditions, such as inflammation.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

- 1 -

TITLE OF THE INVENTION

**SUBSTITUTED PYRIDYL PYRROLES, COMPOSITIONS
CONTAINING SUCH COMPOUNDS AND METHODS OF USE**

5 BACKGROUND OF THE INVENTION

The present invention relates to pyridyl substituted pyrroles. This invention also relates to compositions containing such compounds and methods of treatment.

10 Diabetes is a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose. Uncontrolled hyperglycemia is associated with an increased risk for microvascular and macrovascular diseases, including nephropathy, retinopathy, hypertension, stroke and heart disease. Control of glucose levels is, therefore, a major approach to the treatment of diabetes.

15 Glucagon is a major counter regulatory hormone that attenuates the inhibition of liver gluconeogenesis by insulin. Glucagon receptors are found primarily in the liver, although their presence has been documented in kidney and adipose tissue.

20 Type II diabetics have elevated levels of plasma glucagon and increased rates of hepatic glucose production. The rate of hepatic glucose production positively correlates with fasting blood glucose levels in type II diabetics. Therefore, antagonists of glucagon are useful in improving insulin responsiveness in the liver, decreasing the rate of gluconeogenesis and lowering the rate of hepatic glucose output resulting in a decrease in the levels of plasma glucose.

25 Blood glucose homeostasis is also mediated by the hormone insulin, produced in the β cells of the pancreas. Deterioration of these cells is typically observed in Type I diabetics, and abnormalities in the function of these cells may occur in patients presenting the symptoms of Type II diabetes.

30 Cytokine mediated diseases refers to diseases or conditions in which excessive or unregulated production or activity of one or more cytokines occurs. Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8) and Tumor Necrosis Factor (TNF) are cytokines

produced by a variety of cells, which are involved in immunoregulation and other physiological conditions, such as inflammation.

IL-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions. [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T-helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

There are many disease states in which IL-1 is implicated. Included among these diseases are rheumatoid arthritis, osteoarthritis, endotoxemia, toxic shock syndrome, other acute or chronic inflammatory diseases, such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic β cells.

IL-6 is a cytokine effecting the immune system, hematopoiesis and acute phase reactions. It is produced by several mammalian cell types in response to agents such as IL-1 and is correlated with disease states such as angiofollicular lymphoid hyperplasia.

IL-8 is a chemotactic factor first identified and characterized in 1987. Many different names have been applied to IL-8, such as neutrophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil chemotactic factor (MDNCF), neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor.

Like IL-1, IL-8 is produced by several cell types, including mononuclear cells, fibroblasts, and endothelial cells. Its production is induced by IL-1, TNF and by lipopolysaccharide (LPS). IL-8 stimulates a number of cellular functions in vitro. It is a chemoattractant for neutrophils, T-lymphocytes and basophils. It induces histamine release

- 3 -

from basophils. It causes lysozomal enzyme release and respiratory burst from neutrophils, and it has been shown to increase the surface expression of Mac-1 (CD11b/CD 18) on neutrophils without de novo protein synthesis. The compounds of formula I are also useful in
5 treating diseases characterized by excessive IL-8 activity. There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. These diseases include psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and
10 glomerulonephritis.

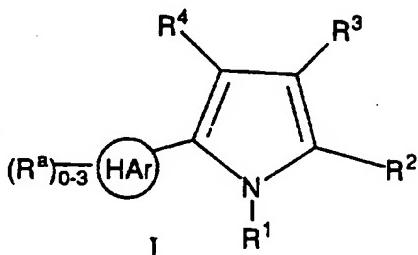
Excessive or unregulated TNF production has been implicated in mediating or exacerbating rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis,
15 toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft v. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia
20 secondary to acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

Cytokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, *et al.*, Proc.
25 Natl. Acad. Sci., 87:782-784 (1990)]. Therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T-cells. TNF has also been implicated in various roles with other viral infections, such as the cytomegalovirus (CMV), influenza virus and the herpes virus.

30 There remains a need for compounds which are cytokine suppressive or antagonistic, i.e., compounds which are capable of interfering with, inhibiting or antagonizing cytokines such as IL-1, IL-6, IL-8 and TNF.

SUMMARY OF THE INVENTION

The present invention is directed to a compound represented by formula I:



5

or a pharmaceutically acceptable salt, solvate, hydrate or tautomer thereof, wherein:

(HAr)

represents a heteroaryl group containing from 5 to

- 10 10 atoms, 1-4 of which are heteroatoms, 0-4 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 0-3 R^a groups;

- 15 each R^a independently represents a member selected from the group consisting of: halo, aryl(R^b)₀₋₂, heteroaryl(R^b)₀₋₂, CF₃, OCF₃, CN, NO₂, R²¹, OR²³; SR²³, S(O)R²³, SO₂R²¹, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, NR²⁰OSO₂R²¹, NR²⁰C(NR²⁰)NHR²³, COR²⁰, CO₂R²³, CONR²⁰R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, SO₂NR²⁰CO₂R²¹, 20 OCONR²⁰R²³, OCONR²⁰SO₂R²¹, C(NR²⁰)NR²⁰R²³, C(O)OCH₂OC(O)R²⁰, CONR²⁰SO₂R²¹ and SO₂NR²⁰CO₂R²¹;

- when present, each R^b independently represents a member selected from the group consisting of: halo, CF₃, OCF₃, CN, NO₂, 25 OR²³; SR²³, S(O)R²³, SO₂R²¹, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, NR²⁰SO₂R²¹, NR²⁰C(NR²⁰)NHR²³, COR²⁰, CO₂R²³, CONR²⁰R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³,

- 5 -

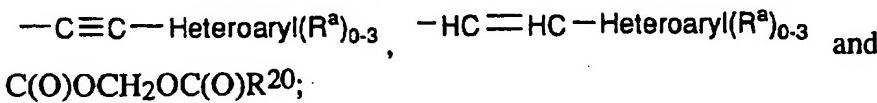
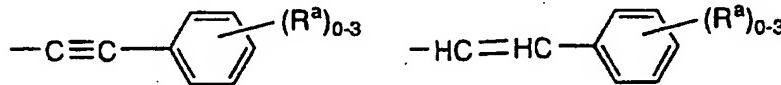
OCONR²⁰SO₂R²¹, C(NR²⁰)NR²⁰R²³, C(O)OCH₂OC(O)R²⁰,
CONR²⁰SO₂R²¹, and SO₂NR²⁰CO₂R²;

- R¹ is selected from the group consisting of: H, aryl, C₁-15
5 alkyl, C₃-15 alkenyl, C₃-15 alkynyl and heterocyclyl, said alkyl, aryl,
alkenyl, alkynyl and heterocyclyl being optionally substituted with from
one to three members selected from the group consisting of: aryl,
heteroaryl, heterocyclyl, halo, OR²³, SR²³, N(R²³)₂, S(O)R²¹, SO₂R²¹,
SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹,
10 NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, COR²⁰,
CO₂R²³, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹,
SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³ and
C(O)OCH₂OC(O)R²⁰;
- 15 R² is selected from the group consisting of: C₁-15 alkyl,
aryl (with the proviso that aryl is not unsubstituted phenyl), heteroaryl
(with the proviso that heteroaryl is not unsubstituted pyridyl), C₇-15
alkenyl, C₂-15 alkynyl, CONR²⁰R²³, SO₂R²¹ (wherein R²¹ is not alkyl
or C₁-6 alkenyl), SO₂N(R²⁰)₂, SO₂NR²⁰COR²¹,
20 SO₂NR²⁰CON(R²⁰)₂, COR²⁰, CO₂R²⁰ (wherein R²⁰ is not C₁-6 alkyl
or hydrogen), CONR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹ and heterocyclyl,
said alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl being
optionally substituted with from one to three members selected from the
group consisting of: halo, C₁-15 alkyl, OCF₃, CF₃, CN, aryl, NO₂,
25 heteroaryl, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂,
SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²²,
NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², COR²⁰, CO₂R²⁰, CON(R²⁰)₂,
CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²²,
and OCONR²⁰R²³;
- 30 R³ is selected from the group consisting of: H, aryl, C₁-15
alkyl, C₂-15 alkenyl, C₂-15 alkynyl, halo, NO₂, CN, CONR²⁰R²³,
SO₂R²¹, SO₂N(R²⁰)₂, SO₂NR²⁰COR²¹, SO₂NR²⁰CON(R²⁰)₂,
COR²⁰, CO₂R²⁰, CONR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹ and

- 6 -

heterocyclyl, said alkyl, alkenyl, alkynyl, aryl, and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: halo, C₁-15 alkyl, CF₃, OCF₃, CN, aryl, NO₂, heteroaryl, OR²³, SR²³, N(R²³)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂,
 5 SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², COR²⁰, CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², OR²⁰ and OCONR²⁰R²³;

10 R⁴ is selected from the group consisting of COR²⁰, COOR²⁰, CONR²⁰R²³, aryl, heterocyclyl, C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl, said alkyl, alkenyl and alkynyl group optionally interrupted by 1-2 oxo or heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and said C₁-15 alkyl, aryl, heterocyclyl, C₃-15 alkenyl, C₃-15
 15 alkynyl being optionally substituted with from 1-3 of R²¹, halo, aryl(R^a)₀₋₃, heteroaryl(R^a)₀₋₃, heterocyclyl, CN, CF₃, NO₂, OR²³, SR²³, NR²⁰R²³, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, OR²⁰CO₂R²³, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, CO₂R²³, COR²⁰,
 20 CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³,



25 R²⁰ represents a member selected from the group consisting of: H, C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl and alkynyl being optionally substituted with 1-3 groups selected from halo, aryl and heteroaryl;

30 R²¹ represents a member selected from the group consisting of: C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl, aryl,

- 7 -

- heterocyclyl and heteroaryl; said alkyl, alkenyl or alkynyl being optionally interrupted by 1-2 heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and said alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl being optionally substituted with from 1-3 of halo,
- 5 heterocyclyl, heteroaryl, aryl(R^a)₀₋₂, heteroaryl(R^a)₀₋₂, CN, OR²⁰, O((CH₂)_nO)_mR²⁰, NR²⁰((CH₂)_nO)_mR²⁰ wherein n represents an integer of from 1 to 4, and m represents an integer of from 1 to 4; SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂,
- 10 NR²²C(NR²²)NHR²², CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², OCONHR²⁰R²³ and OCON(R²⁰)₂;

R²² is selected from the group consisting of: C₁₋₁₅ alkyl,
15 C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or heteroaryl groups;

R²³ is R²¹ or H;

20 R²⁴ is selected from aryl, COR²², CO₂R²², CON(R²⁰)₂ and SO₂R²²; and

when two R²⁰ groups are present, R²⁰ and R²¹ are present, or R²⁰ and R²³ are present, said two R²⁰ groups, R²⁰ and R²¹ or said

25 R²⁰ and R²³ may be taken in combination with the atoms to which they are attached and any intervening atoms and represent heterocyclyl containing from 5-10 atoms, at least one atom of which is a heteroatom selected from O, S or N, said heterocyclyl optionally containing 1-3 additional N atoms and 0-1 additional O or S atom.

30 Also included in the invention is a pharmaceutical composition which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

Also included in the invention is a method of treating diabetic disease, comprising administering to a mammalian patient in need of such treatment an amount of a compound of formula I which is effective to treat said diabetic disease.

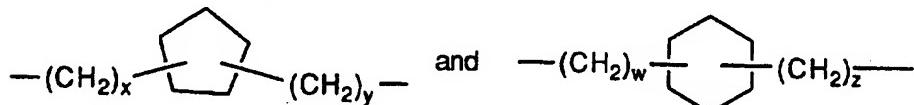
5 Also included in the invention is a method of treating cytokine mediated disease in a mammal, comprising administering to a mammalian patient in need of such treatment an amount of a compound of formula I which is effective to treat said cytokine mediated disease.

10 DETAILED DESCRIPTION OF THE INVENTION

The invention is described herein in detail using the terms defined below unless otherwise specified.

15 The term "alkyl" refers to a monovalent alkane (hydro-carbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred straight or branched alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and t-butyl. Preferred cycloalkyl groups include cyclopentyl and cyclohexyl.

20 Alkyl also includes a straight or branched alkyl group which contains or is interrupted by a cycloalkylene portion. Examples include the following:



wherein: x plus y = from 0-10 and w plus z = from 0-9.

25 The alkylene and monovalent alkyl portion(s) of the alkyl group can be attached at any available point of attachment to the cycloalkylene portion.

30 When substituted, alkyl groups may be substituted with up to three substituent groups, as defined, at any available point of attachment. One of the 15 carbon atoms can be carbonyl. Thus, substitution may be in the straight or branched portion, or in the cycloalkyl portion.

The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 15 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic (non-resonating) carbon-carbon double bonds may be present. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted when a substituted alkenyl group is provided.

10 The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 15 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Preferred alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted when a substituted alkynyl group is provided.

15 Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and like groups as well as rings which are fused, e.g., naphthyl and the like. Aryl thus contains at least one ring having at least 6 atoms, with up to two such rings being present, containing up to 10 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. The preferred aryl groups are phenyl and naphthyl. Aryl groups may likewise be substituted with 1-3 groups selected from 20 R^a. Preferred substituted aryls include phenyl and naphthyl substituted with one or two groups.

25 The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in 30 which one additional carbon atom is optionally replaced by a heteroatom selected from O or S, and/or in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms. The heteroaryl

- 10 -

group is optionally substituted with up to three groups selected from R^a.

Heteroaryl thus includes aromatic and partially aromatic groups which contain one or more heteroatoms. Examples of this type 5 are pyrrole, furan, thiophene, pyridine, oxazole, thiazole and oxazine. Additional nitrogen atoms may be present together with the first 10 nitrogen and oxygen or sulfur, giving, e.g., thiadiazole. The preferred heteroaryls are those where only nitrogen heteroatoms are present when there is more than one. Typical of these are pyrazole, tetrazole, imidazole, pyridine, pyrimidine and pyrazine.

(HAr)

The group (HAr) represents a heteroaryl group which contains from 5 to 10 atoms. One to four atoms are heteroatoms which are selected from O, S and N. The heteroaryl group may be unsubstituted or substituted with 0-3 R^a groups.

15 Preferred heteroaryl groups represented by (HAr) are as follows: pyridyl, quinolyl, purinyl, imidazolyl, imidazopyridinyl and pyrimidinyl.

20 The terms "heterocycloalkyl" and "heterocyclyl" refer to a cycloalkyl group (nonaromatic) in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S or N, and in which up to three additional carbon atoms may be replaced by heteroatoms.

25 The heterocyclyl is carbon or nitrogen linked, if said heterocyclyl is carbon linked and contains a nitrogen, then nitrogen may be substituted by R²⁴. One of the carbon atoms can be carbonyl. Examples of heterocyclyls are piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuran, tetrahydroimidazo[4,5-c]pyridine, imidazolinyl, piperazinyl, pyrrolidine-2-one, piperidin-2-one and the like.

Oxo refers to carbonyl groups -C(O)-.

30 The term "TNF mediated disease or disease state" refer to disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance

- 11 -

is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF.

The term "cytokine" as used herein is meant any secreted 5 polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines regardless of which cells produce them. Examples of cytokines include, but are not limited to, Interleukin-1 10 (IL-1), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF- α) and Tumor Necrosis Factor-beta (TNF- β).

By the term "cytokine antagonizing, interfering or cytokine suppressive amount" is meant an amount of a compound of formula I 15 which will, cause a decrease in the *in vivo* presence or level of the cytokine to normal or sub-normal levels, when given to the patient for the prophylaxis or therapeutic treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production.

The compounds of the present invention may contain one or 20 more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present invention.

Throughout the instant application, the following abbreviations are used with the following meanings:

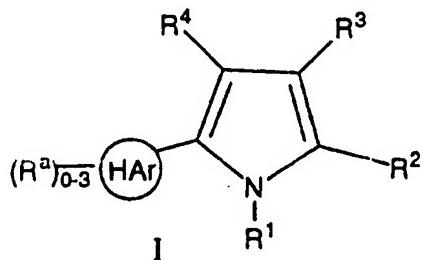
25	aFGF	acid fibroblast growth factor
	Bu	butyl
	Bn	benzyl
	BOC, Boc	t-butyloxycarbonyl
	CBZ, Cbz	Benzylloxycarbonyl
30	DCC	Dicyclohexylcarbodiimide
	DCM	dichloromethane
	DIEA	diisopropylethylamine
	DMF	N,N-dimethylformamide
	DMAP	4-Dimethylaminopyridine

- 12 -

	DTT	dithiothreitol
	EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide hydrochloride
	Et	ethyl
5	EtOAc	ethyl acetate
	EtOH	ethanol
	eq.	equivalent(s)
	FAB-MS	Fast atom bombardment-mass spectroscopy
	HBGF	hemoglobin growth factor
10	HOAc	acetic acid
	HPLC	High pressure liquid chromatography
	HOBT, HOBt	Hydroxybenztriazole
	HS	human serum
	LAH	Lithium aluminum hydride
15	Me	methyl
	NMM	N-Methylmorpholine
	PBS	phosphate buffer saline
	Ph	phenyl
	TFA	Trifluoroacetic acid
20	THF	Tetrahydrofuran
	TMS	Trimethylsilane

- 13 -

The present invention is directed to a compound represented by formula I:



5

or a pharmaceutically acceptable salt, solvate, hydrate or tautomer thereof, wherein:

(HAr)

- represents a heteroaryl group containing from 5 to 10 atoms, 1-4 of which are heteroatoms, 0-4 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 0-3 R^a groups;

- each R^a independently represents a member selected from the group consisting of: halo, aryl(R^b)₀₋₂, heteroaryl(R^b)₀₋₂, CF₃, OCF₃, CN, NO₂, R²¹, OR²³; SR²³, S(O)R²³, SO₂R²¹, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, NR²⁰SO₂R²¹, NR²⁰C(NR²⁰)NHR²³, COR²⁰, CO₂R²³, CONR²⁰R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, C(NR²⁰)NR²⁰R²³, C(O)OCH₂OC(O)R²⁰, CONR²⁰SO₂R²¹ and SO₂NR²⁰CO₂R²¹;

- when present, each R^b independently represents a member selected from the group consisting of: halo, CF₃, OCF₃, CN, NO₂, OR²³; SR²³, S(O)R²³, SO₂R²¹, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, NR²⁰SO₂R²¹, NR²⁰C(NR²⁰)NHR²³, COR²⁰, CO₂R²³, CONR²⁰R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³,

- 14 -

OCONR²⁰SO₂R²¹, C(NR²⁰)NR²⁰R²³, C(O)OCH₂OC(O)R²⁰,
CONR²⁰SO₂R²¹, and SO₂NR²⁰CO₂R²;

R¹ is selected from the group consisting of: H, aryl, C₁-15
5 alkyl, C₃-15 alkenyl, C₃-15 alkynyl and heterocyclyl, said alkyl, aryl,
alkenyl, alkynyl and heterocyclyl being optionally substituted with from
one to three members selected from the group consisting of: aryl,
heteroaryl, heterocyclyl, halo, OR²³, SR²³, N(R²³)₂, S(O)R²¹, SO₂R²¹,
SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹,
10 NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, COR²⁰,
CO₂R²³, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹,
SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³ and
C(O)OCH₂OC(O)R²⁰,

15 R² is selected from the group consisting of: C₁-15 alkyl,
aryl (with the proviso that aryl is not unsubstituted phenyl), heteroaryl
(with the proviso that heteroaryl is not unsubstituted pyridyl), C₇-15
alkenyl, C₂-15 alkynyl, CONR²⁰R²³, SO₂R²¹ (wherein R²¹ is not alkyl
or C₁-6 alkenyl), SO₂N(R²⁰)₂, SO₂NR²⁰COR²¹,
20 SO₂NR²⁰CON(R²⁰)₂, COR²⁰, CO₂R²⁰ (wherein R²⁰ is not C₁-6 alkyl
or hydrogen), CONR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹ and heterocyclyl,
said alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl being
optionally substituted with from one to three members selected from the
group consisting of: halo, C₁-15 alkyl, OCF₃, CF₃, CN, aryl, NO₂,
25 heteroaryl, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂,
SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²²,
NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², COR²⁰, CO₂R²⁰, CON(R²⁰)₂,
CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²²,
and OCONR²⁰R²³;

30 R³ is selected from the group consisting of: H, aryl, C₁-15
alkyl, C₂-15 alkenyl, C₂-15 alkynyl, halo, NO₂, CN, CONR²⁰R²³,
SO₂R²¹, SO₂N(R²⁰)₂, SO₂NR²⁰COR²¹, SO₂NR²⁰CON(R²⁰)₂,
COR²⁰, CO₂R²⁰, CONR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹ and

- 15 -

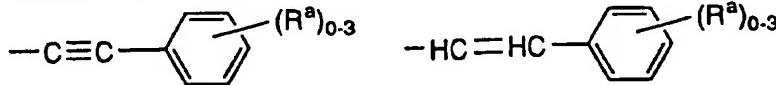
heterocyclyl, said alkyl, alkenyl, alkynyl, aryl, and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: halo, C₁-15 alkyl, CF₃, OCF₃, CN, aryl, NO₂, heteroaryl, OR²³, SR²³, N(R²³)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂,

5 SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², COR²⁰, CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², OR²⁰ and OCONR²⁰R²³;

10 R⁴ is selected from the group consisting of COR²⁰, COOR²⁰, CONR²⁰R²³, aryl, heterocyclyl, C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl, said alkyl, alkenyl and alkynyl group optionally interrupted by 1-2 oxo or heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and said C₁-15 alkyl, aryl, heterocyclyl, C₃-15 alkenyl, C₃-15

15 alkynyl being optionally substituted with from 1-3 of R²¹, halo, aryl(R^a)₀₋₃, heteroaryl(R^a)₀₋₃, heterocyclyl, CN, CF₃, NO₂, OR²³, SR²³, NR²⁰R²³, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, OR²⁰CO₂R²³, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, CO₂R²³, COR²⁰,

20 CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³,



—C≡C—Heteroaryl(R^a)₀₋₃, —HC=HC—Heteroaryl(R^a)₀₋₃ and
C(O)OCH₂OC(O)R²⁰;

25 R²⁰ represents a member selected from the group consisting of: H, C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl and alkynyl being optionally substituted with 1-3 groups selected from halo, aryl and heteroaryl;

30 R²¹ represents a member selected from the group consisting of: C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl, aryl,

- 16 -

heterocyclyl and heteroaryl; said alkyl, alkenyl or alkynyl being optionally interrupted by 1-2 heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and said alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl being optionally substituted with from 1-3 of halo,

- 5 heterocyclyl, heteroaryl, aryl(R^a)₀₋₂, heteroaryl(R^a)₀₋₂, CN, OR²⁰, O((CH₂)_nO)_mR²⁰, NR²⁰((CH₂)_nO)_mR²⁰ wherein n represents an integer of from 1 to 4, and m represents an integer of from 1 to 4; SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂,
- 10 NR²²C(NR²²)NHR²², CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², OCONHR²⁰R²³ and OCON(R²⁰)₂;

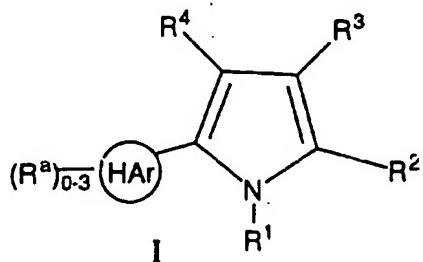
- R²² is selected from the group consisting of: C₁₋₁₅ alkyl,
15 C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or heteroaryl groups;

20 R²³ is R²¹ or H;

R²⁴ is selected from aryl, COR²², CO₂R²², CON(R²⁰)₂ and SO₂R²²; and

25 when two R²⁰ groups are present, R²⁰ and R²¹ are present, or R²⁰ and R²³ are present, said two R²⁰ groups, R²⁰ and R²¹ or said R²⁰ and R²³ may be taken in combination with the atoms to which they are attached and any intervening atoms and represent heterocyclyl containing from 5-10 atoms, at least one atom of which is a heteroatom selected from O, S or N, said heterocyclyl optionally containing 1-3 additional N atoms and 0-1 additional O or S atom.

More particularly, a preferred aspect of the present invention is directed to a compound represented by formula I:



5

or a pharmaceutically acceptable salt thereof, wherein:

(HAr)

- represents a heteroaryl group containing from 5 to 10 atoms, 1-4 of which are heteroatoms, 0-4 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 0-3 Ra groups;

- each Ra independently represents a member selected from the group consisting of: halo, aryl(Rb)0-2, heteroaryl(Rb)0-2, CF₃, OCF₃, CN, NO₂, R²¹, OR²³; SR²³, S(O)R²³, SO₂R²¹, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, NR²⁰SO₂R²¹, NR²⁰C(NR²⁰)NHR²³, COR²⁰, CO₂R²³, CONR²⁰R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, C(NR²⁰)NR²⁰R²³, C(O)OCH₂OC(O)R²⁰, CONR²⁰SO₂R²¹, and SO₂NR²⁰CO₂R²¹;

20

Rb is Ra minus aryl, heteroaryl and R²¹;

- R¹ is selected from the group consisting of: H, aryl, C₁₋₁₅ alkyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl and heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: aryl, heteroaryl, heterocyclyl, halo, OR²³, SR²³, N(R²³)₂, S(O)R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹,

- 18 -

NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, COR²⁰, CO₂R²³, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³ and C(O)OCH₂OC(O)R²⁰;

5

- R² is selected from the group consisting of: aryl (wherein aryl is not unsubstituted phenyl), heteroaryl (wherein heteroaryl is not unsubstituted pyridyl), C₇-15 alkenyl, C₂-15 alkynyl, CONR²⁰R²³, SO₂R²¹ (wherein R²¹ is not alkyl or C₁-6 alkenyl), SO₂N(R²⁰)₂, SO₂NR²⁰COR²¹, SO₂NR²⁰CON(R²⁰)₂, COR²⁰, CO₂R²⁰ (wherein R²⁰ is not C₁-6 alkyl or hydrogen), CONR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹ and heterocyclyl, said alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: halo, C₁-15 alkyl, OCF₃, CF₃, CN, aryl, NO₂, heteroaryl, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², COR²⁰, CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², and OCONR²⁰R²³;

20

- R³ is selected from the group consisting of: H, aryl, C₁-15 alkyl, C₂-15 alkenyl, C₂-15 alkynyl, halo, NO₂, CN, CONR²⁰R²³, SO₂R²¹, SO₂N(R²⁰)₂, SO₂NR²⁰COR²¹, SO₂NR²⁰CON(R²⁰)₂, COR²⁰, CO₂R²⁰, CONR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹ and heterocyclyl, said alkyl, alkenyl, alkynyl, aryl, and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: halo, C₁-15 alkyl, OCF₃, CF₃, CN, aryl, NO₂, heteroaryl, OR²³, SR²³, N(R²³)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², COR²⁰, CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², OR²⁰ and OCONR²⁰R²³;

- R⁴ is selected from the group consisting of COR²⁰, COOR²⁰, CONR²⁰R²³, aryl, heterocycll, C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl, said alkyl, alkenyl and alkynyl group optionally interrupted by 1-2 oxo or heteroatoms selected from O, S, S(O), SO₂ or
- 5 NR²⁴ and said C₁-15 alkyl, aryl, heterocycll, C₃-15 alkenyl, C₃-15 alkynyl being optionally substituted with from 1-3 of R²¹, halo, aryl(R^a)₀₋₃, heteroaryl(R^a)₀₋₃, heterocycll, CN, CF₃, NO₂, OR²³, SR²³, NR²⁰R²³, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, OR²⁰CO₂R²³, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹,
- 10 NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, CO₂R²³, COR²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³ and C(O)OCH₂OC(O)R²⁰;
- 15 R²⁰ represents a member selected from the group consisting of: H, C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl, heterocycll, aryl and heteroaryl, said alkyl, alkenyl and alkynyl being optionally substituted with 1-3 groups selected from halo, aryl and heteroaryl;
- 20 R²¹ represents a member selected from the group consisting of: C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl, aryl, heterocycll and heteroaryl; said alkyl, alkenyl or alkynyl being optionally interrupted by 1-2 heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and said alkyl, alkenyl, alkynyl, aryl, heterocycll and heteroaryl being optionally substituted with from 1-3 of halo, heterocycll, heteroaryl, aryl(R^a)₀₋₂, heteroaryl(R^a)₀₋₂, CN, OR²⁰, O((CH₂)_nO)_mR²⁰, NR²⁰((CH₂)_nO)_mR²⁰ wherein n represents an integer of from 1 to 4, and m represents an integer of from 1 to 4; SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²²,
- 25 SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², OCONHR²⁰R²³ and OCON(R²⁰)₂;

- 20 -

R²² is selected from the group consisting of: C₁₋₁₅ alkyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or heteroaryl groups;

5

R²³ is R²¹ or H;

R²⁴ is selected from aryl, COR²², CO₂R²², CON(R²⁰)₂ and SO₂R²²; and

- 10 in any substituent wherein two R²⁰ groups are present, wherein R²⁰ and R²¹ are present, or wherein R²⁰ and R²³ are present, said two R²⁰ groups, R²⁰ and R²¹ or said R²⁰ and R²³ may be taken in combination with the atoms to which they are attached and any intervening atoms and represent heterocyclyl containing from 5-10 atoms, at least one atom of which is a heteroatom selected from O, S or N, said heterocyclyl optionally containing 1-3 additional N atoms and 0-1 additional O or S atom.
- 15

- 20 A subset of compounds of the invention includes compounds of formula I wherein R¹ represents H, alkyl, substituted alkyl, aryl and substituted aryl, said substituted groups being substituted with from 1 to 3 groups selected from R^a. All other variables of formula I are as originally defined.

- 25 Another subset of compounds of the invention includes compounds of formula I wherein R² represents aryl (wherein aryl is not unsubstituted phenyl), heteroaryl (wherein heteroaryl is not unsubstituted pyridyl), C₁₋₁₅ alkyl, C₇₋₁₅ alkenyl, C₂₋₁₅ alkynyl, and heterocyclyl, said alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl groups being unsubstituted or substituted with 1 to 3 groups of R^a. All other variables of formula I are as originally defined.

30 Another subset of compounds of the invention includes compounds of formula I wherein R³ represents H, alkyl, halo, NO₂, CN, CONR²⁰R²³, SO₂R²¹ and CO₂R²⁰, said alkyl group being

- 21 -

unsubstituted or substituted with 1 to 3 groups of R^a. All other variables of formula I are as originally defined.

Another subset of compounds of the invention includes compounds of formula I wherein R⁴ is aryl, alkyl, alkenyl, alkynyl, heterocyclyl, CO₂R²⁰ or CONR²⁰R²³, said aryl, alkyl, alkenyl, alkynyl, and heterocyclyl being unsubstituted or substituted with 1 to 3 groups of R^a. All other variables of formula I are as originally defined.

Another subset of compounds of the invention includes compounds of formula I wherein Har represents a member selected from the group consisting of: pyridinyl, quinolyl, purinyl, imidazolyl, imidazopyridinyl, pyrimidinyl, pyrrolyl, triazolyl and the like.

More particularly, a subset of compounds of the present invention includes compounds of formula I wherein Har represents a member selected from the following:

- 15 a) pyridinyl,
- b) quinolyl,
- c) purinyl,
- d) imidazolyl,
- e) imidazopyridinyl and
- 20 f) pyrimidinyl.

Within this subset, all other variables are as originally defined.

More particularly, Har represents 3- or 4- pyridinyl. All other variables of formula I are as originally defined.

Another group of compounds of particular interest relates to compounds of formula I having from 1-3 R^a groups attached to the Har substituent. Each R^a is independently selected from the group consisting of: halo, aryl(R^b)₀₋₂, heteroaryl(R^b)₀₋₂, CF₃, OCF₃, NO₂, R²¹, OR²³; SR²³, S(O)R²³, SO₂R²¹, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, NR²⁰SO₂R²¹, SO₂NR²⁰R²³, 30 SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³ and SO₂NR²⁰CO₂R²¹, and when present, each R^b, R²⁰, R²¹ R²², R²³ and R²⁴ is as originally defined.

Another set of compounds of formula I is that wherein:
35 R¹ is H, aryl, or C₁₋₁₅ alkyl;

- 22 -

R² is aryl (wherein aryl is not unsubstituted phenyl), heteroaryl (wherein heteroaryl is not unsubstituted pyridyl), C₇₋₁₅ alkenyl, C₂₋₁₅ alkynyl, heterocyclyl;

5 R³ is H, halo, NO₂, CO₂R²⁰, CONHiPr or CN; and

R⁴ is aryl, C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, CO₂R²⁰, CONR²⁰R²³ or heterocyclyl, said aryl, alkyl and heterocyclyl being unsubstituted or substituted with 1 to 3 groups of R^a.

10 Another set of compounds of formula I is that wherein:

R¹ is H or aryl;

15 R² is aryl (wherein aryl is not unsubstituted phenyl), heteroaryl (wherein heteroaryl is not unsubstituted pyridyl), or heterocyclyl;

R³ is H or halo;

20 R⁴ is aryl, C_{1-C6} alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, CO₂R²⁰, heterocyclyl or CONR²⁰R²³, said aryl, alkyl and heterocyclyl being unsubstituted or substituted with 1 to 3 groups of R^a and

25 HAr is a) pyridinyl,
b) quinolyl,
c) purinyl,
d) imidazolyl,
e) imidazopyridinyl or
f) pyrimidinyl.

30 A preferred set of compounds of formula I is that wherein:

(R^a)₀₋₃-HAr is:

- a) 4-pyridinyl,
- b) 2-(methyl)-4-pyridinyl,
- c) 3-(methyl)-4-pyridinyl,
- d) 2-(amino)-4-pyridinyl,
- 5 e) 2-(benzylamino)-4-pyridinyl,
- f) 2-(acetylamino)-4-pyridinyl,
- g) 4-quinolinyl-,
- h) 4-(3-F)-quinolinyl,
- i) 2-imidazo-(4,5-b)-pyridinyl,
- 10 j) 7-imidazo-(4,3-b)-pyridinyl,
- k) 2-imidazo-(4,5-b)-pyridinyl,
- l) 4-(2-F)-pyridinyl,
- m) 4-(3-F)-pyridinyl,
- n) 4-(2-SMe)-pyrimidinyl,
- 15 o) 4-(2-NH₂)-pyrimidinyl,
- p) 4-(2-MeNH)-pyrimidinyl,
- q) 2-(NH₂)-pyridinyl,
- r) 2-(MeNH)-pyridinyl,
- s) 2-(N-benzylamino)pyridinyl,
- 20 t) 3-pyridinyl,
- u) 2-pyridinyl or
- v) 4-(2,6-di-phenyl)-pyridinyl;

R¹ is H or 2-(OH)-Phenyl;

- 25 R² is
- 1) Cl-Ph,
 - 2) Br-Ph,
 - 3) F-Ph,
 - 4) (C₁-C₄ alkyl)-Ph,
 - 5) CF₃-Ph
 - 6) (O-(C₁-C₄ alkyl))-Ph,
 - 7) (C₃-C₆ cycloalkyl)-Ph,
 - 8) phenyl-Ph,
 - 30 9) CN-Ph,

- 24 -

- 10) COOH-Ph,
11) NO₂-Ph,
12) SMe-Ph,
13) (O-phenyl)-Ph,
5 14) (S-phenyl)-Ph,
15) (OBn)-Ph,
16) -(S(O)-phenyl)-Ph,
17) OCF₃-Ph,
18) CO₂Et-Ph,
10 19) -S(O)Me-Ph,
20) (CH₂NH₂)-Ph,
21) NH₂-Ph,
22) N-CBz-piperdin-4-yl,
23) N-Me-piperdin-4-yl,
15 24) t-butyl-Ph,
25) 2-thiophenyl,
26) 3,4-(OCH₂O)-Ph,
27) 3-(Cl)-4-(F)-Ph,
28) -S(O)Ph,
20 29) 2,4-(Cl)-Phenyl,
30) 3,4-(Cl)-Phenyl,
31) 2-(OMe)-4-(Cl)Ph,
32) 4-N-(acetyl)-piperidinyl,
33) 4-N-(OMe-CO)-piperidinyl,
25 34) 4-N-(iPr-CO)-piperidinyl,
35) 4-piperidinyl,
36) 4-pyridinyl,
37) c-hexyl,
38) 4-(OBn)-Phenyl,
30 39) 4-N(CO₂Me)-piperidinyl or
40) 3-(Me)-4-(F)-Phenyl;

R³ is H, Br or Cl;

- 25 -

- R⁴ is
1. 4-(phenyl)-Ph,
 2. 3-(phenyl)-Ph,
 3. 4-(2-thiophenyl)-Ph,
 4. 4-(t-butyl)-Ph,
 5. 4-(toluyl)-Ph,
 6. 4-(4-fluorophenyl)-Ph,
 7. 4-(3-nitro-phenyl)-Ph,
 8. 3-(3-nitro-phenyl)-Ph,
 9. 4-(quinolinyl)-Ph,
 10. Cl-Ph,
 11. OMe-Ph,
 12. Br-Ph,
 13. CF₃-Ph,
 14. (cyclohexyl)-Ph,
 15. (i-butyl)-Ph,
 16. (4-(2-tetrazol-5-yl)-phenyl)-Ph,
 17. 4-(3-thiophenyl)-Ph,
 18. 2-(naphthyl)-Ph,
 19. F-Ph,
 20. hydroxy-Ph,
 21. 4-NMe₂-Ph,
 22. CO₂Et-Ph,
 23. COOH-Ph,
 24. 4(OMe)-Ph,
 25. 2-(F)-4-(Br)-Ph,
 26. 4-(4-CF₃-phenyl)-Ph,
 27. 4-(4-OMe-phenyl)-Ph,
 28. 3-(4-OMe-phenyl)-Ph,
 29. 4-(1-naphthyl)-Ph,
 30. phenyl,
 31. 4-(4-Me-Ph)-Ph,
 32. 3-(2-thiophenyl)-Ph,
 33. 3-(3-thiophenyl)-Ph,
 34. 4-(3-(iBu)-6-(SO₂NH₂)-Ph)-Ph,

35. 4-(3-(iBu)-6-(SO₂NH₂t-Bu)-Ph)-Ph,
36. 4-(4-(nBu)-Ph)-Ph,
37. 4-(3-(iBu)-6-(SO₂NHCO₂nBu)-Ph)-Ph,
38. 3-(4-(n-Bu)-Ph)-Ph,
5. 39. 4-(3-(n-Pr)-6-(tetrazol-5-yl)-Ph)-Ph,
40. 4-(5-n-Bu)-thiophenyl-Ph,
41. 2-F-4-(2-(5-n-Bu)-thiophenyl)-Ph,
42. 3,5-(2-thiophenyl)phenyl,
43. 3,4-(4-OMe-Ph)-Ph,
10. 44. 3,5-(4-Me-Ph)-Ph,
45. 3,5-(4-SMe-Ph)-Ph,
46. 4-(NHCOMe)-Ph,
47. 4-(OCH₂CO₂Me)-Ph,
48. 3,5-(di-Bromo)-Ph,
15. 49. 4-(iPr)-Ph,
50. 4-(OBn)-Ph,
51. 2-(OPr)-Ph,
52. -CONHBn,
53. -CON-((4-benzyl)-piperidinyl),
20. 54. -CONHPh,
55. -CO-(4-N-phenyl-piperizin-1-yl),
56. -CONH-((2-(2-indolyl)-phenyl),
57. -CONH-4-biphenyl,
58. -CONH-2-biphenyl,
25. 59. 3,5-(3-nitrophenyl)-phenyl,
60. 4-(2-benzofuranyl)-phenyl,
61. 3-Br-5-(2-thiophenyl)-phenyl,
62. 4-(2-(5-Cl)-thiophenyl)-phenyl,
63. 4-(3,5-(CF₃)-phenyl)-phenyl,
30. 64. 4-(2-(OMe)-phenyl)-phenyl,
65. 4-(4-Cl-phenyl)-phenyl,
66. 4-(CO₂Me)-phenyl,
67. 2-F-4-(2-thiophenyl)-phenyl,
68. 4-(3-(NH₂)-phenyl)-phenyl,

- 27 -

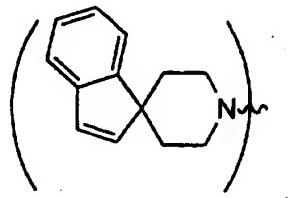
69. 4-(3-(OMe)-phenyl)-phenyl,
70. 2,6-F-Ph,
71. -CONH-2-fluorenyl,
72. -CONH-(4-(n-octyl)-phenyl),
- 5 73. -CONH-adamantyl,
74. -CONH-c-hexyl,
75. -CONH-CH(Bn)2,
76. -CONHCH(Ph)2,
77. -CONHCH₂CH-(Ph)2,
- 10 78. -CONH-2-tetrahydro-isoquinolinyl,
79. -CO₂Bn,
80. 3-(OBn)-Ph,
81. 4-(CHCH-Ph)-Ph,
82. 9-phenanthrenyl,
- 15 83. 3-(OPh)-Ph,
84. 2-(OMe)-Ph,
85. CO₂Et,
86. COOH,
87. 4-CN-Phenyl,
- 20 88. 2,4-F-Phenyl,
89. 2,4,6,-F-Phenyl,
90. 2-(3-OMe-Ph)-Ph,
91. 2-(3-NO₂-Ph)-Ph,
92. 2-(thiophen-2-yl)-Ph,
- 25 93. 2-(OEt)-Ph,
94. 2-(OH)-5-(Br)-Ph,
95. 2-(OMe)-5-(Br)-Ph,
96. 2,5-(OMe)-Ph,
97. 4-(tetrazol-5-yl)-Ph,
- 30 98. 2-F-(4-(Cl)-thiophen-2-yl)-Ph,
99. 4-(CONHtBu)-Ph,
100. 4-(N-methyl-tetrazol-5-yl)-Ph,
101. 2-(Cl)-4-(Br)-Ph,
102. 2-(ethoxy)-5-(Br)-Ph,

- 28 -

- 103. 2,5-F-Ph,
- 104. 2-(3-(Cl)-propoxy)-Ph,
- 105. 2-(propoxy)-5-(Br)-Ph,
- 106. 2-(F)-5-(Br)-Ph,
- 5 107. 4-(CON(Bn₂))-Ph,
- 108. 4-(3-Pyr)-Ph,
- 109. 4-(CO-(N-Boc-piperazin)-Ph,
- 110. 4-(CONPn₂)-Ph,
- 111. 4-(CO-morpholinyl)-Ph,
- 10 112. 4-(CO-L-proline-OtBu)-Ph,
- 113. 4-(CO-spiroindane-1)-Ph,
- 114. 4-(CO-spiroindene-1)-Ph,
- 115. 4-(CON(Me)₂)-Ph,
- 116. 4-(heterocycle-1)-Ph,
- 15 117. 4-(heterocycle-2)-Ph,
- 118. CO₂-(2-Ph-Ph),
- 119. CHCHPh,
- 120. 2-(OBn)-Ph,
- 121. 2-(O-hexyl)-Ph,
- 20 122. 2-(O-nonyl)-Ph,
- 123. 2-(O-iPr)-Ph,
- 124. 2-(O-iBu)-Ph,
- 125. 4-(2-pyr)-Ph,
- 126. 4-(2-SO₂NH₂tBu-Ph)-2-F-Ph
- 25 127. 4-NO₂-Ph,
- 128. 4-NH₂-Ph or
- 129. 4-(NHCO₂-butyl)-Ph

wherein:

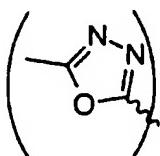
spiroindene-1 is:



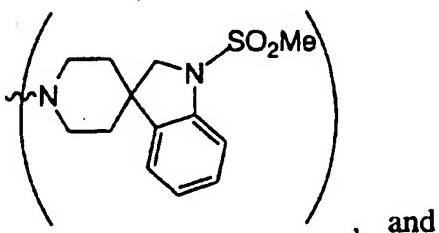
30

- 29 -

heterocycle-1 is:

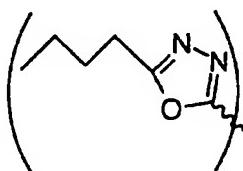


5 spiroindane-1 is:



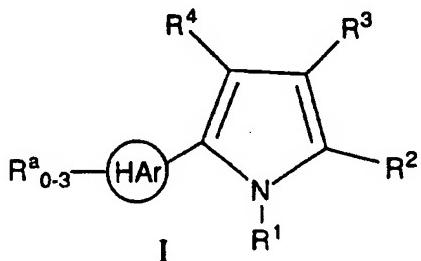
, and

heterocycle-2 is:



10

A further set of compounds includes compounds represented by formula:



15

or a pharmaceutically acceptable salt thereof, wherein:

- 30 -

(HAr)

represents a heteroaryl group containing from 5 to 10 atoms, 1-3 of which are heteroatoms, 0-3 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being substituted with 1-3 R^a groups;

5

each R^a independently represents a member selected from the group consisting of: halo; CN, NO₂, R²¹; OR²³; SR²³; S(O)R²¹; SO₂R²¹; NR²⁰R²³; NR²⁰COR²¹; NR²⁰CO₂R²¹; NR²⁰CONR²⁰R²³; NR²⁰SO₂R²¹; NR²⁰C(NR²⁰)NHR²³, CO₂R²³; CONR²⁰R²³;

10 SO₂NR²⁰R²³; SO₂NR²⁰COR²¹; SO₂NR²⁰CONR²⁰R²³; SO₂NR²⁰CO₂R²¹; OCONR²⁰R²³; OCONR²⁰SO₂R²⁰, C(NR²⁰)NR²⁰R²³; C(O)OCH₂OC(O)R²⁰; CONR²⁰SO₂R²¹; and SO₂NR²⁰CO₂R²¹, tetrazol-5-yl;

15

R¹ is selected from the group consisting of: H, aryl, C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl; and heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: aryl, heteroaryl, heterocyclyl, halo, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, CO₂R²³, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³ and C(O)OCH₂OC(O)R²⁰;

25

R² is selected from the group consisting of: aryl, heteroaryl, heterocyclyl, C₁-15 alkyl, C₂-15 alkenyl, C₂-15 alkynyl, said alkyl, alkenyl and alkynyl group optionally interrupted by 1-2 heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and said aryl,

30 heteroaryl, heterocyclyl, alkyl, alkenyl, alkynyl being optionally substituted with from 1-3 of halo, aryl, heteroaryl, aryl(R^a)₁₋₂, C₁-15 alkyl, heteroaryl(R^a)₁₋₂, CN, CF₃, NO₂, heterocyclyl, OR²³, SR²³, NR²⁰R²³, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹,

$\text{SO}_2\text{NR}^{20}\text{CONR}^{20}\text{R}^{23}$, $\text{NR}^{20}\text{COR}^{21}$, $\text{NR}^{20}\text{CO}_2\text{R}^{21}$, $\text{NR}^{20}\text{CONR}^{20}\text{R}^{23}$,
 $\text{N}(\text{R}^{20})\text{C}(\text{NR}^{20})\text{NHR}^{23}$, CO_2R^{23} , COR^{21} , $\text{CONR}^{20}\text{R}^{23}$,
 $\text{CONR}^{20}\text{SO}_2\text{R}^{21}$, $\text{NR}^{20}\text{SO}_2\text{R}^{21}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{21}$, $\text{OCONR}^{20}\text{R}^{23}$,
 $\text{OCONR}^{20}\text{SO}_2\text{R}^{21}$, $\text{OCONR}^{20}\text{R}^{23}$ and $\text{C}(\text{O})\text{OCH}_2\text{OC}(\text{O})\text{R}^{20}$;

5

R^3 is selected from the group consisting of: H, C₁₋₁₅ alkyl, aryl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, halo, NO₂, CO₂R²², CN, CONR²⁰R²³, SO₂R²¹, SO₂N(R²⁰)₂, SO₂NR²⁰COR²¹, SO₂NR²⁰CON(R²⁰)₂, COR²¹, CO₂R²⁰, CONR²⁰SO₂R²¹,

- 10 $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{21}$, and heterocyclyl, said alkyl, alkenyl, alkynyl, aryl, and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: halo, C₁₋₁₅ alkyl, CF₃, CN, aryl, NO₂, heteroaryl, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²²,
15 NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², OR²⁰ and OCONR²⁰R²³;

R^4 is selected from the group consisting of COR²¹,

- 20 CONR²⁰R²³, aryl, heteroaryl, heterocyclyl, C₁₋₁₅ alkyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl, said alkyl, alkenyl and alkynyl group optionally interrupted by 1-2 heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and said aryl, heteroaryl, heterocyclyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl being optionally substituted with from 1-3 of R²¹, halo, CN, CF₃, NO₂, OR²³, SR²³, NR²⁰R²³, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³,
25 SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, CO₂R²³, COR²¹, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³ and
30 C(O)OCH₂OC(O)R²⁰; said alkyl being optionally substituted with aryl, heteroaryl, heterocyclyl, being optionally substituted with from 1-3 of R²¹, halo, CN, CF₃, NO₂, OR²³, SR²³, NR²⁰R²³, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, CO₂R²³,

COR²¹, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³ and C(O)OCH₂OC(O)R²⁰;

- 5 R²⁰ represents a member selected from the group consisting of: H, C₁₋₁₅ alkyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl and alkynyl being optionally substituted with 1-3 groups selected from halo, aryl and heteroaryl;
- 10 R²¹ represents a member selected from the group consisting of: C₁₋₁₅ alkyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl, aryl, heterocyclyl and heteroaryl; said alkyl, alkenyl or alkynyl being optionally interrupted by 1-2 heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and said alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl being optionally substituted with 1-3 of halo, heterocyclyl, aryl, heteroaryl, aryl(R^a)₁₋₂, heteroaryl(R^a)₁₋₂, CN, OR²⁰, O((CH₂)_nO)_mR²⁰, NR²⁰((CH₂)_nO)_mR²⁰ wherein n represents an integer of from 2 to 4, and m represents an integer of from 1 to 3; SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²²,
- 15 20 SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², OCONHR²⁰R²³ and OCON(R²⁰)₂;
- 25 R²² is selected from the group consisting of: C₁₋₁₅ alkyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or heteroaryl groups;
- 30 R²³ is R²¹ or H;
- R²⁴ is selected from aryl, COR²², CO₂R²², CON(R²⁰)₂ and SO₂R²²;
- n is 1-4;

m is 1-4;

- and in a functional group substituent wherein two R²⁰ groups are present, when R²⁰ and R²¹ are present, or when R²⁰ and R²³ are present, said two R²⁰ groups, R²⁰ and R²¹ or said R²⁰ and R²³ may be taken in combination with the atoms to which they are attached and any intervening atoms and represent heterocyclyl containing from 5-10 atoms, at least one atom of which is a heteroatom selected from O, S or N, said heterocyclyl optionally containing 1-3 additional N atoms
- 5 R²⁰ and 0-1 additional O or S atom.
- 10 Another subset of compounds in accordance with claim 1 is realized when:

15 R¹ is H, aryl or C₁-15 alkyl, wherein H, aryl and C₁-15 alkyl are defined above;

20 R² is aryl, C₁-15 alkyl, heteroaryl or heterocyclyl, wherein aryl, C₁-15 alkyl, heteroaryl and heterocyclyl are defined above;

25 R³ is H, halo, NO₂ or CN; and

R⁴ is aryl, C₁-15 alkyl, heteroaryl, COR²¹, CONR²⁰R²³ or heterocyclyl, wherein aryl, C₁-15 alkyl, heteroaryl, COR²¹, CONR²⁰R²³ or heterocyclyl are defined above.

Still another subset of compounds in accordance with claim 1 is realized when:

30 R¹ is H, or substituted alkyl;

R² is aryl, C₁-C₆- alkyl, heteroaryl, or heterocyclyl; wherein aryl, C₁-C₆ alkyl, heteroaryl, and heterocyclyl are defined above;

R⁴ is aryl, C₁-C₆ alkyl, heteroaryl, heterocyclyl, or CONR²⁰R²³; wherein aryl, C₁-C₆ alkyl, heteroaryl, R²⁰ and R²³ and heterocyclyl are defined above;

5

R³ is H or halo; and

HAr is

- a) pyridyl,
- b) quinolyl,
- c) purinyl,
- d) imidazolyl,
- e) imidazopyridinyl, or
- f) pyrimidinyl.

15

Still a further subset of compounds in accordance with claim 1 is realized when:

HAr is

- a) 4-pyridyl-,
- b) (2-methyl-4-pyridyl)-,
- c) (3-methyl-4-pyridyl)-,
- d) (2-amino-4-pyridyl)-,
- e) (2-benzylamino-4-pyridyl)-,
- f) (2-acetylamino-4-pyridyl)-,
- g) 4-quinolyl-,
- h) (4-(2-methoxy)-pyridyl)-,
- i) 4-pyrimidinyl-,
- j) 9-purinyl-, or
- k) 7-(imidazo[4,5-b]pyridinyl)-;

R¹ is H;

30

R² is phenyl substituted with:

- a) Cl,
- b) Br,
- c) F,

- 35 -

- 5 d) C₁-C₄ alkyl,
 e) CF₃,
 f) O-(C₁-C₄ alkyl),
 g) C₃-C₆ cycloalkyl,
 h) phenyl,
 i) CN,
 j) COOH,
 k) NO₂, or
 l) alkyl-N(alkyl)²;
10 m) NHCO-alkyl
 n) CONHalkyl

- R³ is H
- 15 R⁴ is a) phenyl optionally substituted with:
 1. 4-phenyl,
 2. 3-phenyl,
 3. 4-(2-thiophenyl),
 4. 4-t-butyl,
 5. 4-toluyl,
 6. 4-(4-fluorophenyl)-,
 7. 4-(3-nitrophenyl)-,
 8. 3-(3-nitrophenyl)-,
 9. 4-quinolinyl,
 10. Cl,
 11. OMe,
 12. Br,
 13. CF₃,
 14. cyclohexyl,
 15. butyl,
 16. (4-(2-tetrazol-5-yl)-phenyl)-,
 17. 4-(3-thiophenyl)-, or
 18. 2-naphthyl-;

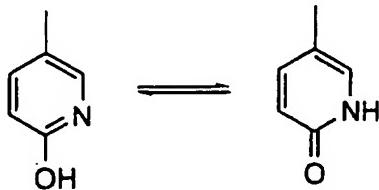
- b) 1. CONH-phenyl
2. CONH-4-biphenyl; and
3. CH₂-phenyl,
4. CH₂-4-(biphenyl), or
5. CH₂-4-(2'-carboxy-biphenyl).

The pharmaceutically acceptable salts of the compounds of formula I include the conventional non-toxic salts or the quaternary ammonium salts of the compounds of formula I formed e.g. from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention.

The compounds of the present invention also may have different tautomeric forms. For example, when Har-(R^a)₀₋₃ represents a 4-hydroxy-3-pyridyl group, the following tautomers are equivalent and within the present invention:



Numerous other tautomeric structures are contemplated as falling within the invention.

- 5 This invention relates to method of antagonizing or inhibiting the production or activity of glucagon, thereby reducing the rate of gluconeogenesis and the concentration of glucose in plasma.

10 The compounds of formula I can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of disease states in mammals caused by elevated levels of glucose.

15 This invention also relates to a method of inhibiting or antagonizing the production or activity of cytokines in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula I to antagonize or inhibit cytokine production or activity, such that it is regulated down to normal levels, or in some cases to subnormal levels, so as to ameliorate or prevent the disease state.

20 The compounds of formula I can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of disease states in mammals, which are exacerbated or caused by excessive or unregulated cytokine production, more specifically IL-1, IL-6, IL-8 or TNF production, by such mammal's cells, such as but not limited to monocytes and/or macrophages.

25 Compounds of formula I inhibit cytokines, such as IL-1, IL-6, IL-8 and TNF and are therefore useful for treating inflammatory diseases such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions.

- The compounds of formula I may be used to treat other disease states mediated by excessive or unregulated cytokine production or activity. Such diseases include, but are not limited to sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome,
- 5 adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy,
- 10 cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDs related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, AIDS and other viral infections, such as cytomegalovirus (CMV), influenza virus, and the herpes family of viruses such as Herpes Zoster or Simplex I and II.
- 15 The compounds of formula I may also be used topically in the treatment of inflammation such as for the treatment of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; inflamed joints, eczema, psoriasis and other inflammatory skin conditions such as sunburn; inflammatory eye
- 20 conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.
- Interleukin-1 (IL-1) has been demonstrated to mediate a variety of biological activities thought to be important in immuno-regulation and other physiological conditions. [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.
- 25 There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced

by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic β cells.

The compounds of formula I are also useful in treating diseases characterized by excessive IL-8 activity. There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. These diseases include psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. The invention includes a method of treating psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis, in a mammal in need of such treatment which comprises administering to said mammal a compound of formula I in an amount which is effective for treating said disease or condition.

The compounds of formula I are normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. This invention, therefore, also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier or diluent. The compounds of formula I are administered in conventional dosage forms prepared by combining a compound of formula I with standard pharmaceutical carriers according to conventional procedures. The compounds of formula I may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, solid or liquid. Solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Liquid carriers include syrup, peanut oil, olive oil, water and the

- 40 -

like. Similarly, the carrier may include time delay material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be in the form of a 5 tablet, hard gelatin capsule, troche or lozenge. The amount of solid will vary widely but preferably will be from about 0.025 mg to about 1 g. When a liquid carrier is used, the preparation is typically in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid or nonaqueous liquid suspension.

10 The compounds of formula I may also be administered topically in the form of a liquid, solid or semi-solid. Liquids include solutions, suspensions and emulsions. Solids include powders, poultices and the like. Semi-solids include creams, ointments, gels and the like.

15 The amount of a compound of formula I, for the methods of use disclosed herein, vary with the compound chosen, the nature and severity of the condition, and other factors left to the discretion of the physician. A representative, topical, anti inflammatory dose of a compound of formula I is from about 0.01 mg to about 1500 mg, administered one to four, preferably one to two times daily.

20 While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient typically comprises about 0.001% to about 90% w/w.

25 Drops according to the present invention may comprise sterile aqueous or oil solutions or suspensions, and may be prepared by dissolving the active ingredient in a suitable aqueous solution, optionally including a bactericidal and/or fungicidal agent and/or any other suitable preservative, and optionally including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a 30 suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%),

benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

- Lotions according to the present invention include those
- 5 suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or
- 10 acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

- Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous liquid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn,
- 15 arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or macrogels. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof.
- 20 25 Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicas, and other ingredients such as lanolin may also be included.

- The methods of the instant invention may be carried out by delivering the monokine activity interfering agent parenterally. The term 'parenteral' as used herein includes intravenous, intramuscular, intradermal and subcutaneous administration. The intravenous and intramuscular forms of administration are preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. The instant invention can also be carried out by delivering

- 42 -

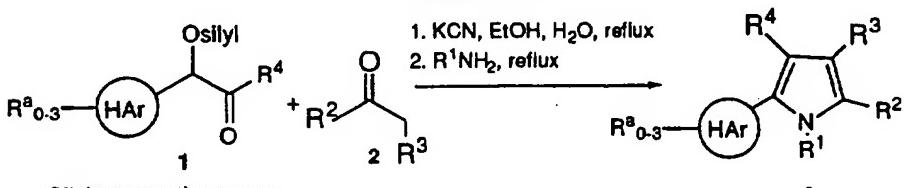
the compound of formula I intranasally, rectally, transdermally or vaginally.

The compounds of formula I may also be administered by inhalation. By 'inhalation' is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

Specific examples of formula I may require the use of protecting groups to enable their successful elaboration into the desired structure.

Compounds of formula I may be prepared by the reaction of a benzoin 1, or protected version thereof with a methyl ketone 2 (commercially available or prepared by well established methods) in the presence of potassium cyanide followed by treatment with an alkyl or aryl amine or ammonia or equivalent thereof (ammonium acetate) at elevated temperature (Ceraulo, L. et al, J. Heterocyclic Chemistry 27, 255, 1990). See Scheme I

Scheme I



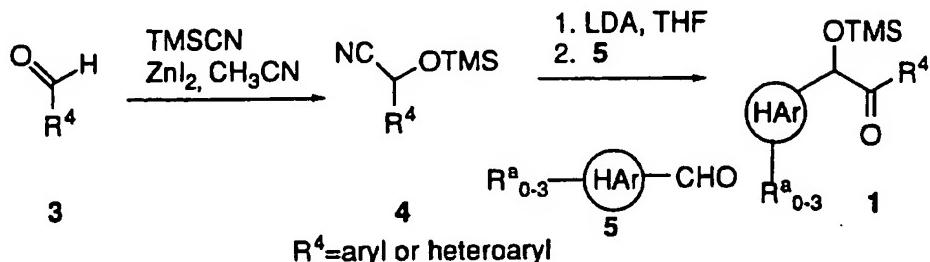
20

Silyl= protecting group
such as t-butyl dimethylsilyl or trimethylsilyl

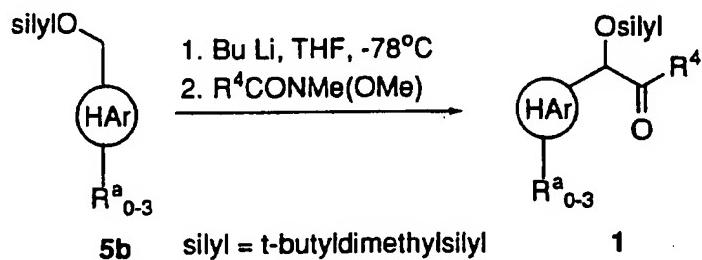
R¹, R², R³ and R⁴ are described above.

Compound 1 is prepared as described below. Aldehydes 3 may be converted to their trimethylsilyl cyanohydrins 4. Deprotonation 25 and reaction with an aldehyde 5 will provide trimethyl silyl protected benzoins 1 (Hunig, S.; Wehner, G. Chem. Ber. 112, 2062 1979).

- 43 -

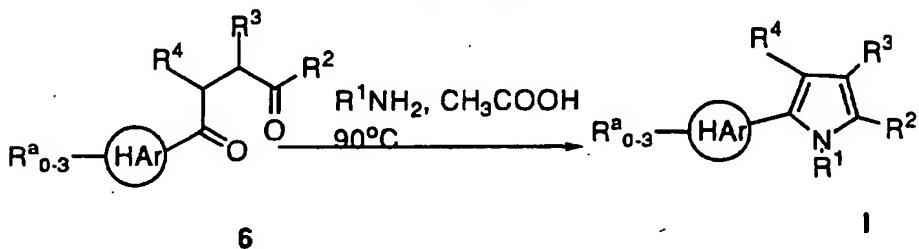


- 5 A protected heteroaryl methyl alcohol **5b** may be deprotonated with a base such as n-butyl lithium in a polar aprotic solvent such as THF at a low temperature. Reaction of this anion with a Weinreb amide will provide alpha-hydroxy ketones **1**.



- 10 The condensation of a 1,4-diketone with ammonia gives rise to pyrroles (Paal Knor Synthesis). A 1,4 diketone such as **6** may be reacted with ammonia (or a compound that gives rise to ammonia such as ammonium acetate) or a primary amine to provide compounds of formula I generally in the presence of an acid catalyst such as acetic acid or titanium tetrachloride at an elevated temperature. See Scheme II
- 15

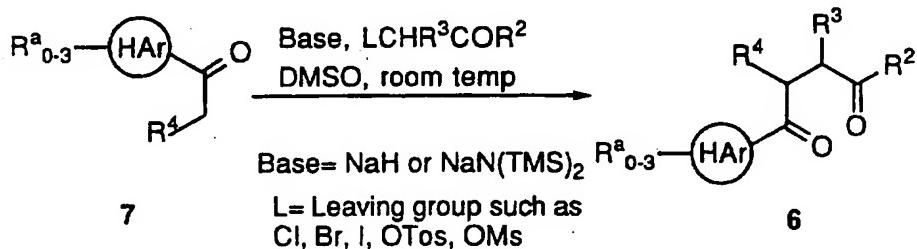
Scheme II



- 44 -

wherein R¹, R², R³ and R⁴ are described above.

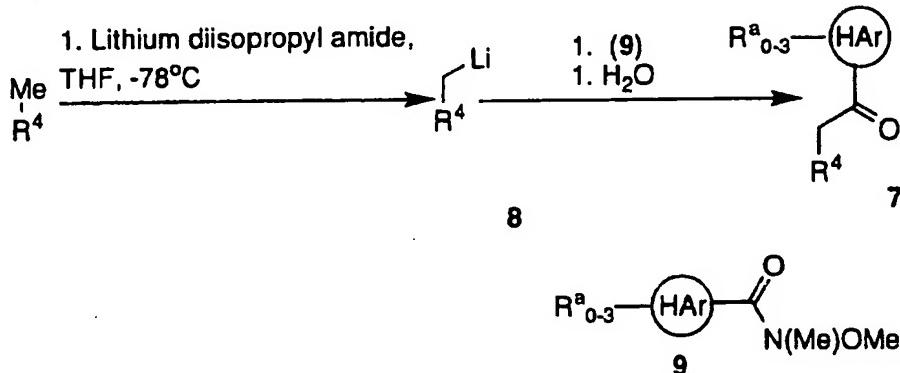
1,4 diketones 6 may be regioselectively constructed so that the appropriate groups are present on the pyrrole ring. Alkylation of 5 1,2-disubstituted heteroarylethanones 7 with bromoacetophenones or other leaving group substituted acetophenones provides 1,4 diketones 6. (Iyer, R. N.; Gopalachari, R. *Ind. J. Chem.* 11, 1260, 1973). Bromo-10 acetophenones are readily prepared by bromination of acetophenones (for example by treatment with bromine in acetic acid or benzyl-trimethylammonium bromide). Chloroketones may be prepared by treatment of activated (mixed anhydride) carboxylic acids with diazomethane followed by hydrogen chloride.



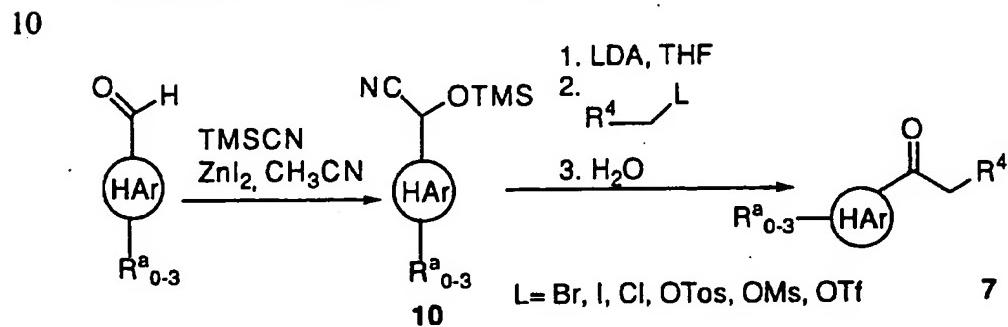
15

Ethanones 7 may be prepared by addition of anions 8 (derived by deprotonation of heteroaryl substituted methyl groups, lithium halogen exchange of alkyl halides, or trialkyltin lithium exchange) to activated benzoic acids 9 (for example esters, acid chlorides, nitriles and N-methoxy-N-methyl amides) (see: Wolfe, J. F. et al J. Org. Chem. 39, 2006 1974 and Kaiser, E. M. et al. Synthesis 705 1975 and Ohsawa A. Chem. Pharm. Bull. 26, 3633, 1978).

- 45 -

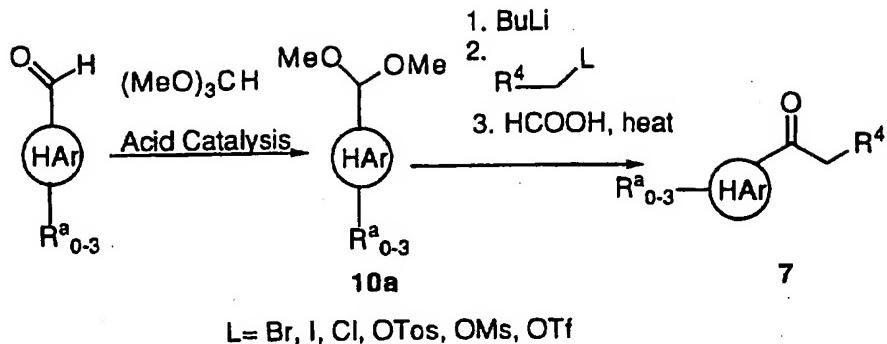


5 7 may also be prepared by alkylation of heteroaryl trimethyl silyl protected cyanohydrins 10. Treatment of 10 with lithium diisopropyl amide in THF and addition of a heteroaryl methyl group functionalized with a leaving group L (for example:Br, I, Cl , tosylate, mesylate) followed by acid catalyzed hydrolysis of the silyl cyanohydrin group will provide ethanones such as 7 (Deuchert, K.; Hertenstein, U.; Hunig, S.; Wehner, G. *Chem. Ber.* **112**, 2045, 1979).



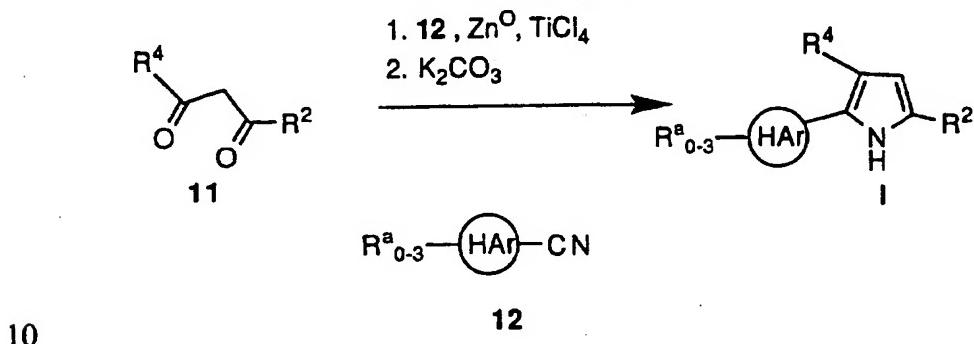
7 may also be prepared by alkylation of the acetal 10a under standard conditions. 10a may be prepared from heteroaryl aldehydes by treatment with $(MeO)_3CH$ under acid catalysis.

- 46 -



The reductive cross coupling of 1,3 diketones **11** with a nitrile **12** in the presence of zinc and titanium tetrachloride may give rise to compounds of formula I (Gao, J. Hu, M.; Chen, J.; Yuan, S.; Chen, W. *Tet Lett.* 34, 1617, 1993). 1,3 diketones **11** may be prepared by alkylation of **4** with bromoacetophenones. See Scheme III.

Scheme III



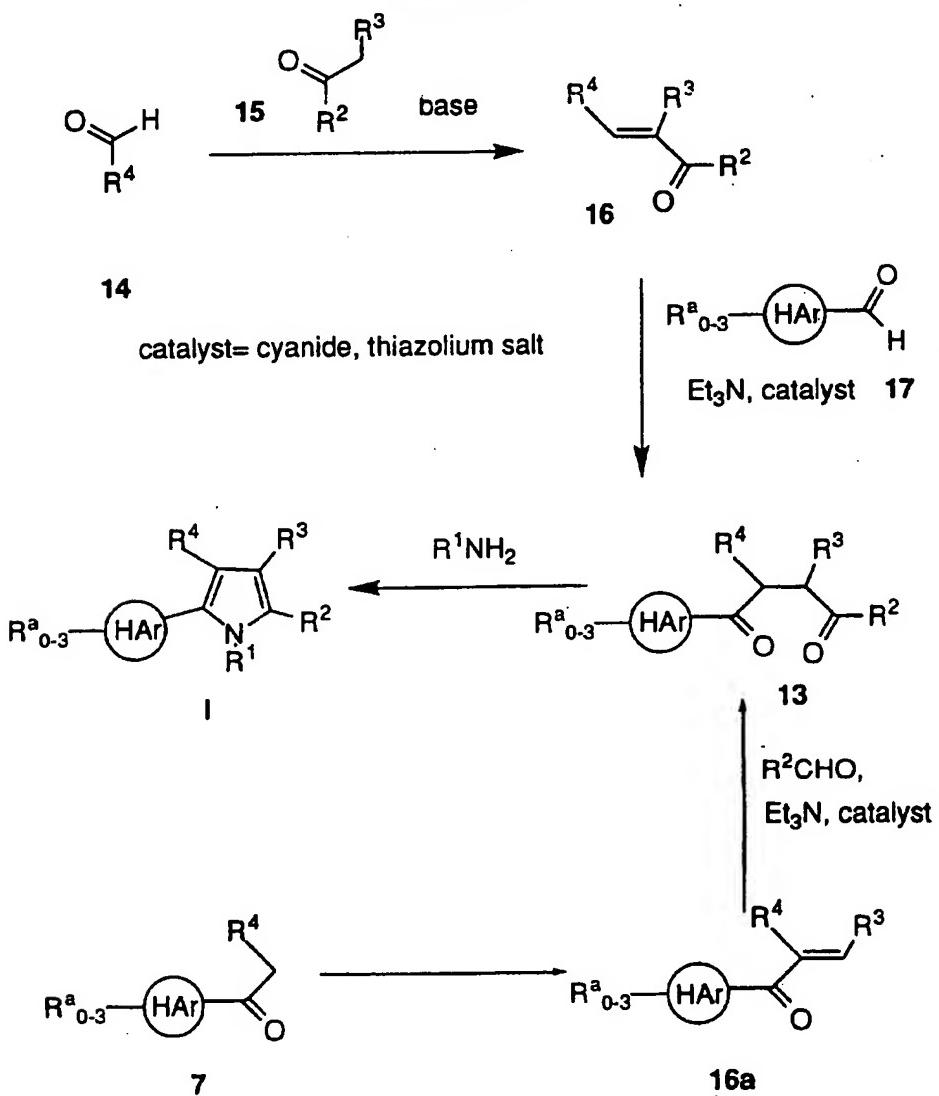
wherein R^2 , and R^4 are described above.

1,4 diketones 13 may also be prepared as described below.
An aldehyde 14 may be condensed in the presence of a base (for
example pyridine and diethylamine or sodium hydroxide) with a methyl
ketone 15 to provide an a,b-unsaturated ketone 16. In the presence of a
catalyst such as cyanide or a thiazolium salt a heteroaryl aldehyde 17
will react with 16 to give 13 (Stetter, H. J. Kuhlmann, H. Organic
reactions 40, 407-496 Heterocyclic Chem. 14, 573, 1977).
Condensation of 13 with an amine will provide compounds of formula

- 47 -

I. Alternatively, 7 may be condensed in the presence of a base with an aldehyde followed by dehydration to give 16a. Reaction of 16a with an aldehyde as before will give 13. See Scheme IV

5

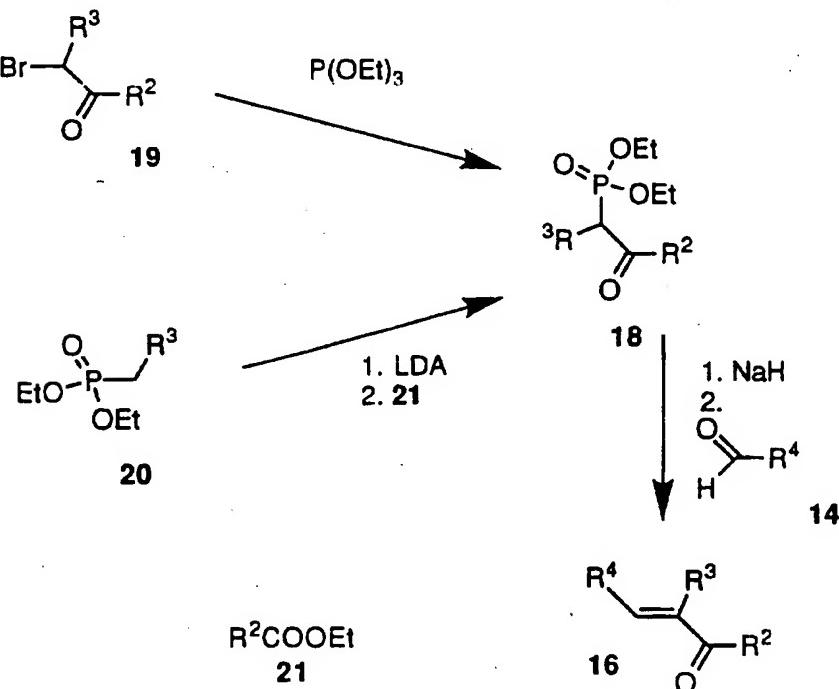
Scheme IV

wherein R¹, R², R³ and R⁴ are described above.

- 48 -

Intermediate 16 may be prepared by the Horner-Emmons reaction of the anion of 18 with the aldehyde 14. The reagent 18 may be prepared by reaction of the bromoketone 19 and triethyl phosphite or by reaction of the lithium salt of diethyl methylphosphonate with an ester 21.

5

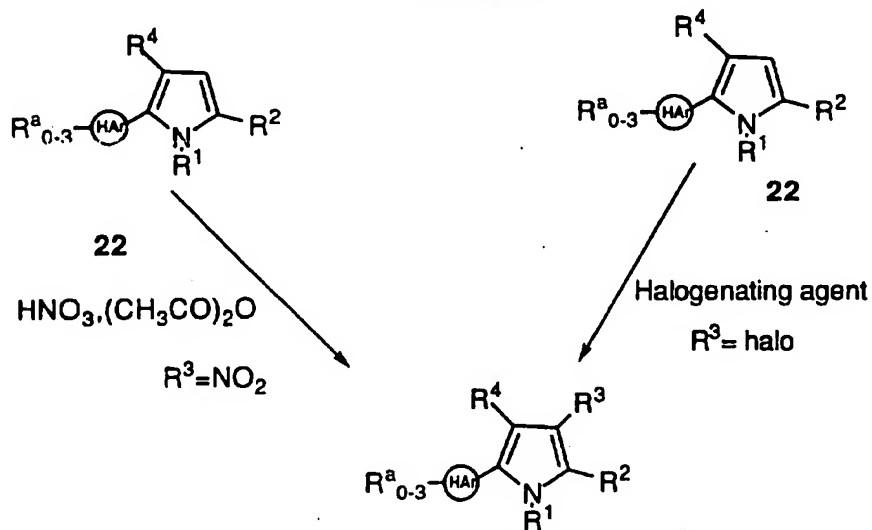


- The nitro group may be introduced into the pyrrole nucleus at the R^3 position (generic nomenclature) by electrophilic
- 10 nitration of a compound such as 22 (or a less advanced intermediate) in the presence of fuming nitric acid and acetic anhydride (Pyrroles Part 1, R. Alan Jones,ed., Heterocyclic Compounds ,Vol 48 Part 1, John Wiley, New York, 1990. Pages 330-345). Halogens may be introduced by electrophilic halogeneration with reagents such as XeF_2 ($\text{R}^2=\text{F}$), N-
- 15 chlorosuccinimide in DMF ($\text{R}^2=\text{Cl}$), N-bromosuccinimide in DMF ($\text{R}^3=\text{Br}$), I_2 in KI ($\text{R}^2=\text{I}$). Other reagents are available to carry out this conversion, the choice of reagent being dependent on the presence of functional groups that may be sensitive to the reagent being utilized

- 49 -

((Pyrroles Part 1, R. Alan Jones,ed., Heterocyclic Compounds ,Vol 48 Part 1, John Wiley, New York, 1990. Pages 348-391). See Scheme V

Scheme V

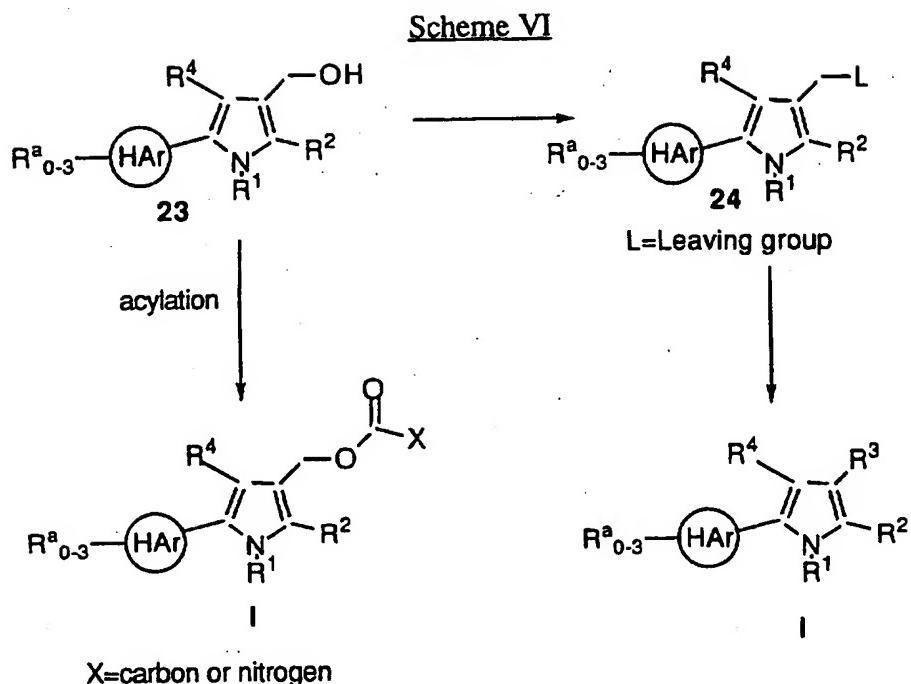


5

wherein R¹, R², R³ and R⁴ are described above.

Introduction of alkyl and heterocyclyl alkyl groups at R³ is described below. Direct introduction is possible as described in 10 the use of 1,4 diketones 6 as a precursor of compounds of formula I as described above. The preparation of a pyrrole containing a hydroxy methyl group 23 at R³ would provide an intermediate that could be readily elaborated into compounds of formula I. Acylation of the hydroxyl group with activated acids or isocyanates would provide esters 15 and carbamates respectively of formula I. Conversion of the hydroxy group into a leaving group 24 (for example Br, I, Cl, triflate etc.) would enable the introduction of alkyl, heterocyclyl and amines and thiol groups by displacement with a nucleophile. The nucleophile could be, for example, an alkyl or heterocyclyl anion, a primary or secondary 20 amine or a thiol. Functional group interconversions known to those skilled in the art would provide compounds of formula I. See Scheme VI

- 50 -

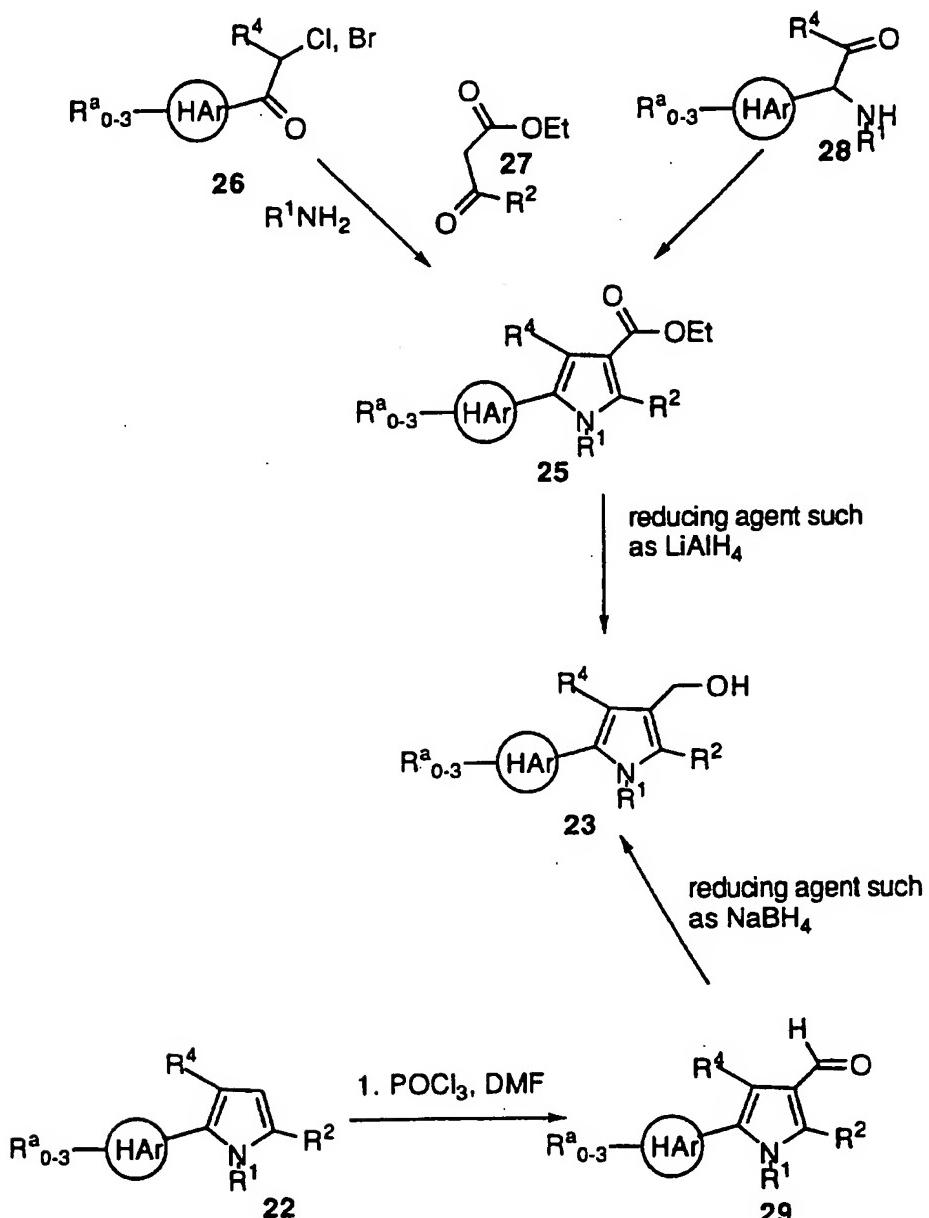


5 wherein R^1 , R^2 , R^3 and R^4 are described above.

Hydroxymethyl substituted pyrroles 23 may be prepared by reduction of esters 25 by reducing agents such as lithium aluminum hydride. The esters 25 may be prepared by classical techniques.

- 10 Treatment of 1,2 disubstituted-2 halo ketones 26 with 3-keto esters 27 with ammonia or amines gives esters 25 (Hantzsch. Ber. Dtsch. Chem. Ges. 23, 1474, 1890). Alternatively, 2-amino ketones 28 react with 3-keto esters 27 to give 25. A further method of synthesis of 23 is via reduction of the aldehyde 29 with a reducing agent such as sodium borohydride. The aldehyde may be prepared by treatment of the R^3 -unsubstituted pyrrole with the Vilsmeier reagent (POCl_3/DMF).
- 15

- 51 -



The pyrrole 22 may be silylated on nitrogen to give 30 by treatment with a silyl chloride and base in a solvent such as 5 methylene chloride. The pyrrole 30 may then be sulphinylated with a

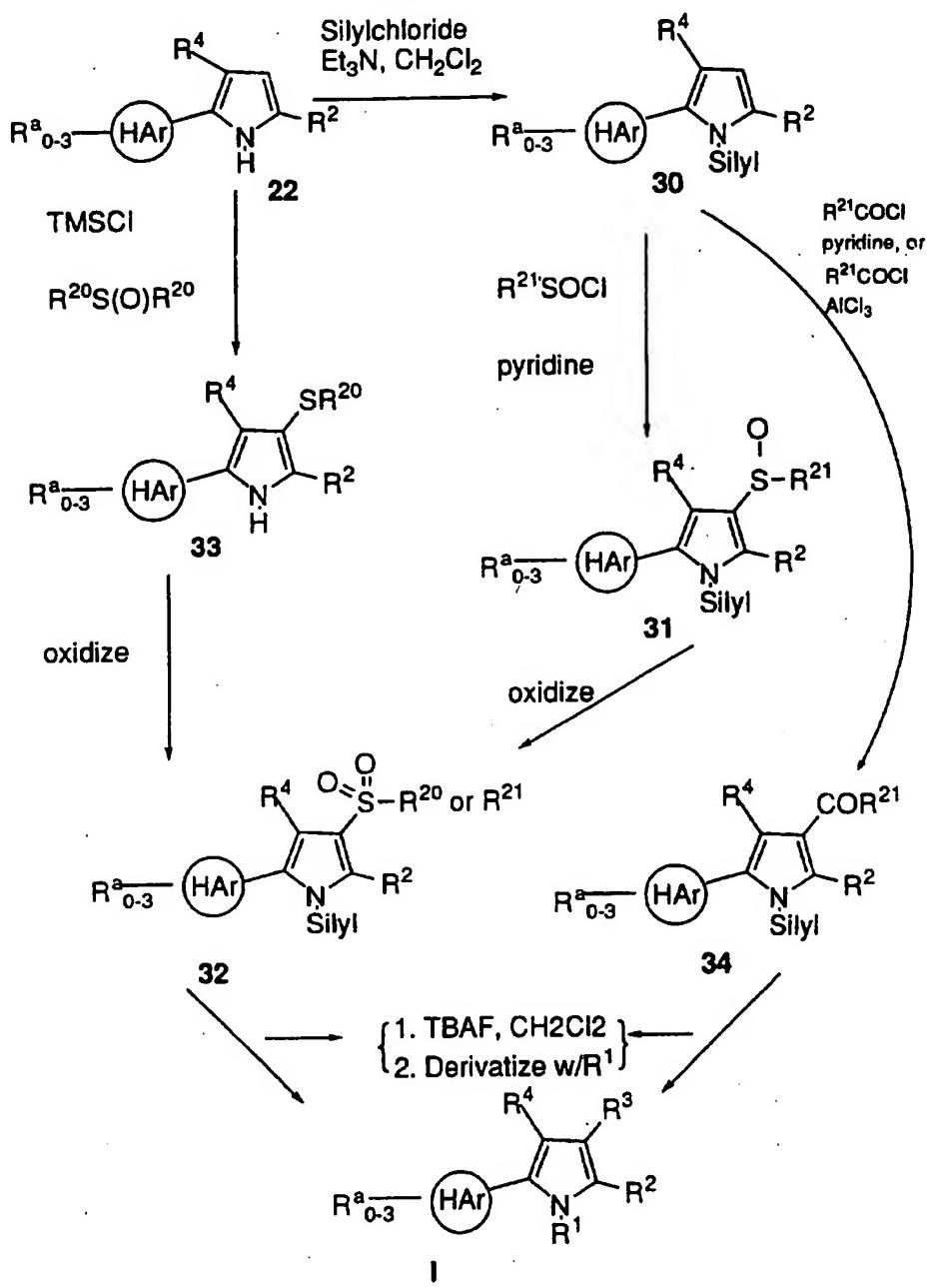
- 52 -

sulphinyllchloride under basic conditions to provide 31 (J. Org. Chem. 6317, 1990). Oxidation of 31 with a reagent such as m-chloroperoxybenzoic acid will give the sulphone 32. Removal of the silyl group and derivatization of the pyrrole will give compounds of Formula 1. 22

- 5 may also be converted to the sulphide 33 by reaction of 22 with a symmetrical sulfoxide in the presence of trimethylsilylchloride. Oxidation of 33 with a reagent such as m-chloroperoxybenzoic acid will give 32. The silyl pyrrole 30 may also be acylated with an acid chloride to give the ketone 34. Removal of the silyl group from 34 and derivatization 10 of the pyrrole will give compounds of Formula 1. Pyrroles such as 22 may also be sulphinylated directly without N-protection, by treatment with sulphinyll chlorides in a solvent such as dichloromethane at 0°C (J. Org. Chem. 5336, 1980). Oxidation as described above may provide pyrroles of Formula 1 where R³ is SO₂R²⁰ or 21. See Scheme
15 VII

- 53 -

SCHEME VII

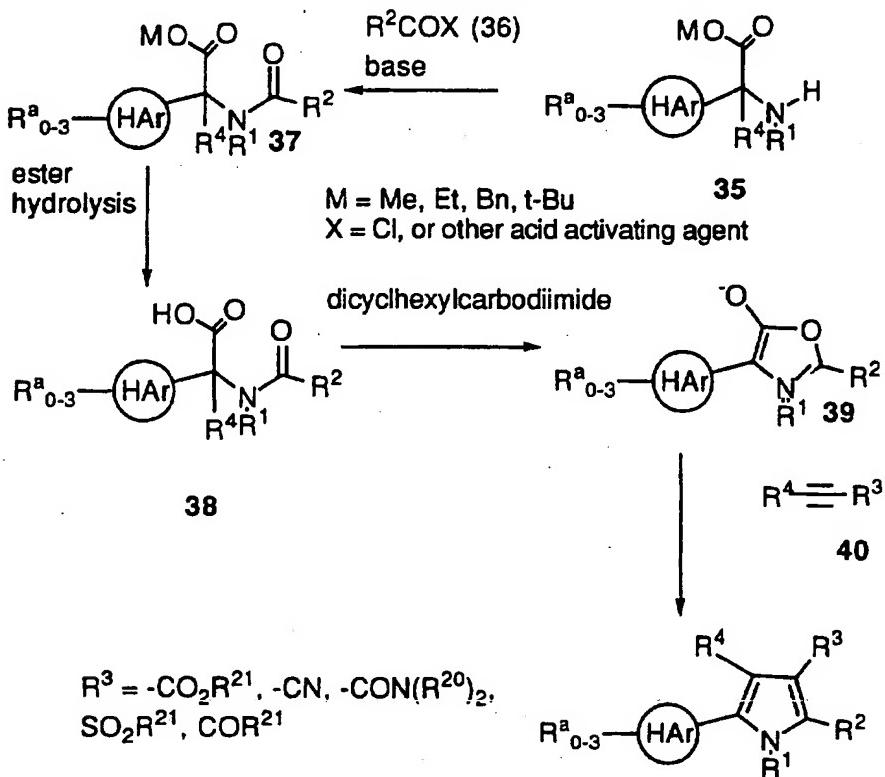


- 54 -

The amino acid ester 35 may be acylated with an acid 36 that is suitably activated (acid chloride or other activating group used in amide coupling reactions) to give 37. Hydrolysis of the ester protecting group will provide 38. Cyclization by treatment with an acid activating group such as DCC will give the oxazolium species 39. Addition of an alkyne 40 to 39 will give a pyrrole of Formula I via a 3+2 cyclo-addition followed by loss of carbon dioxide. Various R³ groups may be incorporated in this manner. See Scheme VIII.

10

SCHEME VIII

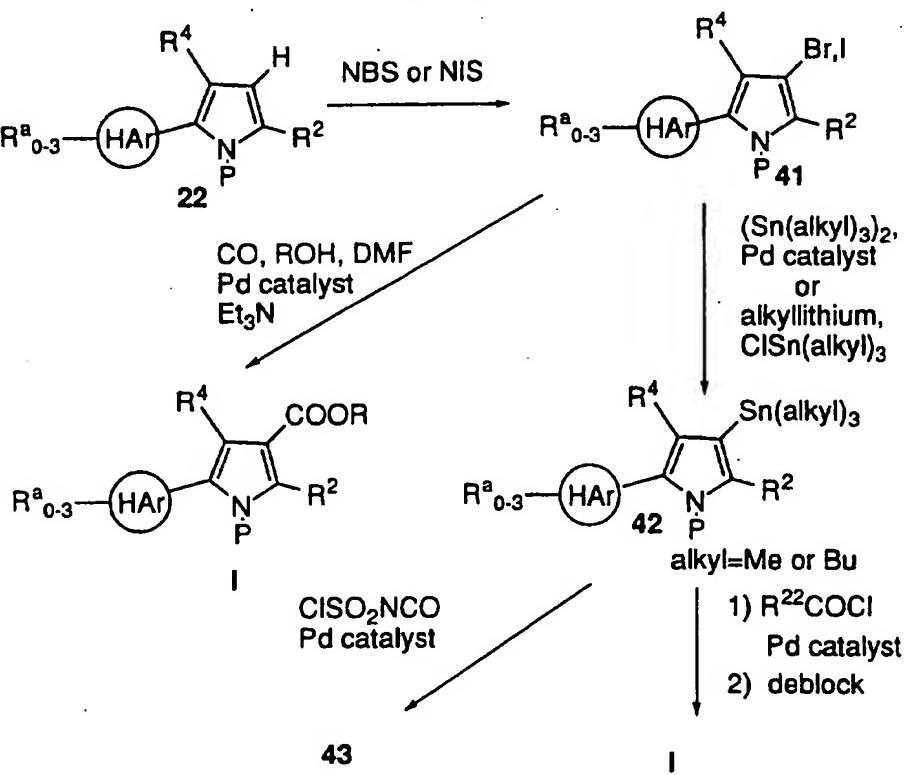


Coupling chemistry may be utilized to introduce R³ groups as shown below in Scheme IX. 4-unsubstituted pyrroles optionally protected at nitrogen (P) 22 may be halogenated by treatment with electrophilic sources of bromine and iodine to provide 41. The halogen

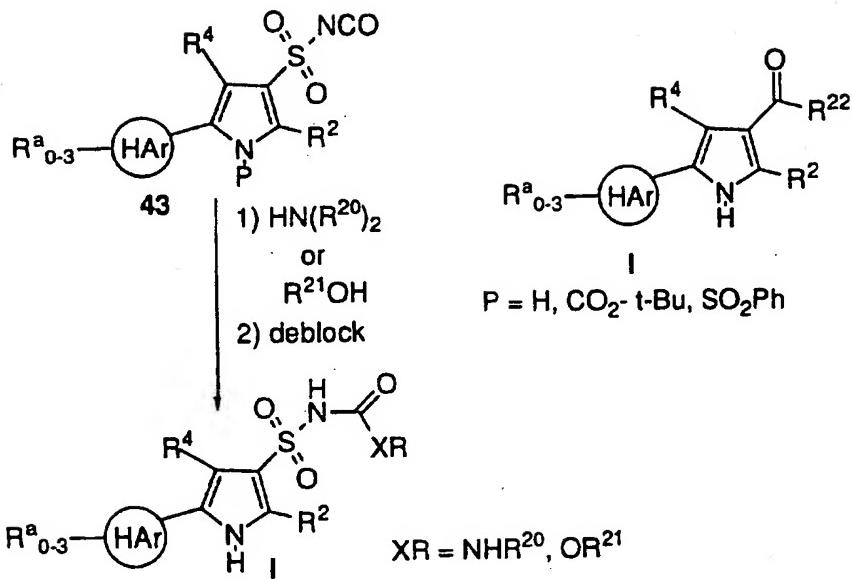
15

may then be coupled with carbon monoxide in the presence of an alcohol to give, after removal of the protecting group, 4-alkoxy-carbonyl substituted pyrroles of formula I. Treatment of 41 with a hexalkylditin in the presence of a palladium catalyst (see above for examples of catalysts) will give the stannylyl pyrrole 42. Alternatively, halogen metal exchange through treatment of 41 with an alkyl lithium followed by addition of a trialkyltinchloride will give 42. The stannylyl pyrrole may then be coupled to acid chlorides to give ketones of formula I after deblocking, if required. Reaction of 42 with chlorosulfonylisocyanate in the presence of a palladium catalyst will give the sulphonyl isocyanate 43. 43 may subsequently be converted to a sulphonyl urea or sulphonyl carbamate of formula I by addition of a primary or secondary amine or an alcohol after deblocking (acid conditions for P = CO₂-t-Bu; basic hydrolysis for P = SO₂Ph), if required.

SCHEME IX

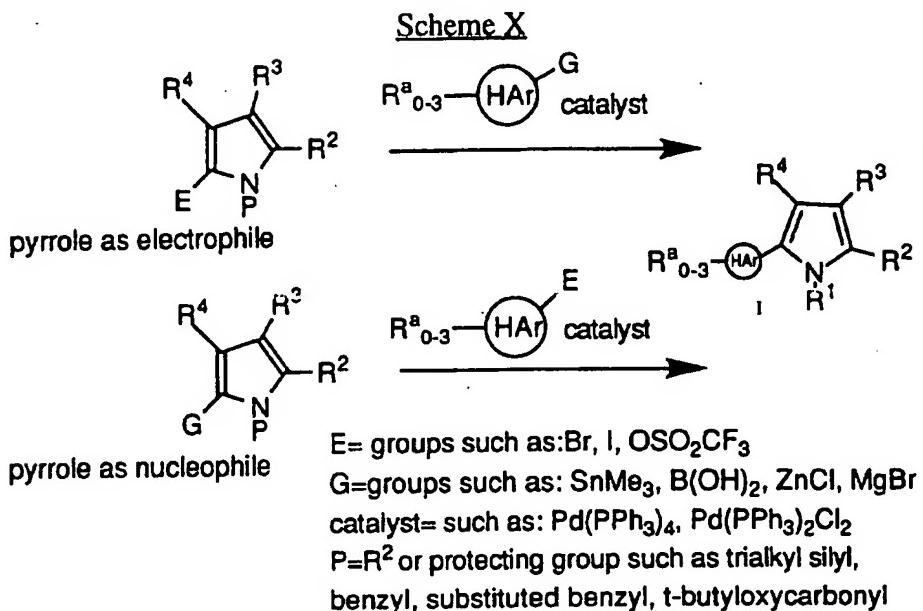


- 56 -



Heteroaryl rings may be appended to a pyrrole ring system by utilization of organometallic coupling technology (Kalinin, V. Synthesis 413 1991). Two alternative approaches may be utilized for appending heteroaryl rings to the pyrrole ring. The pyrrole ring may function as the electrophile or as the nucleophile as illustrated in Scheme X below:

- 57 -



wherein R¹, R², R³ and R⁴ are described above.

5 Any appended aromatic or heteroaromatic rings may be attached to the pyrrole ring system (Alvarez, A. J. et al *J. Org. Chem.* 1653, 1992 (use of boronic acid and tributyl stannanes for coupling to aromatic and heteroaromatic rings)). Attachment of pyrrole pendant groups may be carried out with or without other HAr, R², R³ or R⁴ groups attached.

10 15 20 The synthesis of pyrroles containing nucleophilic groups for coupling reactions depends on the pyrrole substitution pattern. Lithium anions are prepared by metalation of a regioselectively halogenated pyrrole, or the regioselective deprotonation of the pyrrole preferably by the use of a directing functional group. The resulting anion may then be trapped by a trialkyl stannylic halide or a trialkyl borate or transmetalated to magnesium or zinc by treatment with appropriate halide salts. A further method used to incorporate a trialkyl stannylic group is the coupling of a bromo, iodo or triflate substituted pyrrole with hexaalkylditin in the presence of a palladium catalyst.

The synthesis of pyrroles incorporating electrophilic groups may be carried out by the regioselective halogenation of a

pyrrole (Pyrroles Part 1, R. Alan Jones,ed., Heterocyclic Compounds, Vol 48 Part 1, John Wiley, New York, 349-391, 1990). The regioselectivity of halogenation will depend on the size, nature and substitution position on the pyrrole ring as well as the presence or absence of the N-alkyl protecting group. Triflates may be prepared by acylation of hydroxy pyrroles with triflic anhydride.

The reaction conditions used will depend on the nature of the coupling species. In the case of magnesium, zinc and stannyl coupling reactions the solvent used is normally toluene or DMF under anhydrous conditions. In the case of boronic acid couplings, a heterogeneous system is used of water, toluene, dimethoxyethane or ethanol in the presence of a base such as sodium carbonate or bicarbonate. In general the reaction takes place at an elevated temperature (80-100 °C). Catalysts used depend on the structure of the components to be coupled as well as the functional groups. Most commonly, tetrakis(triphenylphosphine)palladium (0) or palladium bis triphenyl phosphine dichloride are utilized.

Coupling of alkenes or alkynes with 4-halo pyrroles (Heck reaction, see Kalinin, V. Synthesis 413 1991 for a review) will give rise to R² (generic nomenclature) alkenyl and alkynyl substituted pyrroles that may be reduced or otherwise modified to provide compounds of formula I.

Substituents of the pendant groups of the pyrrole ring system are prepared utilizing methods well known to those skilled in the art. For example, functional groups such as halogens, sulfides, nitro groups, ethers and other groups stable to the reaction conditions used in the linear synthesis of the pyrroles are incorporated in the initial steps of the reaction sequence. Sulfides may be oxidized to sulfoxides and sulfones with reagents such as m-chloroperbenzoic acid. Sulfides may also be converted to sulfonyl chlorides by oxidation and chlorination by chlorine in water. Primary amines are prepared from nitro groups by catalytic (Pd/C, H₂ or Raney Nickel, H₂) or chemical means (CoCl₂, NaBH₄). Alkylation of amines to give secondary and tertiary amines

is achieved by reductive alkylation (aldehyde, NaCNBH₄) or alkylation with an alkyl group substituted with a leaving group in the presence of a base such as K₂CO₃. Tertiary amines may, alternatively, be carried through the reaction sequence to the pyrroles. Acylation of primary or secondary amines with activated acids, achloroformates, isocyanates and chlorosulfonates will give rise to amides, carbamates, ureas and sulonamides respectively.

- Other methods of preparing amides and ureas are useful; treatment of the amine with phosgene, or an equivalent thereof, followed by acylation of an alcohol or amine with the intermediate activated chloroformamide. Carboxylic acids are best introduced as esters early in the synthesis. Saponification will provide carboxylic acids. Transesterification or esterification of the acids will give esters. Carboxylic acids may be converted to amides by activation and reaction with amines. Phenols are best introduced in a protected form early in the synthetic sequence to the pyrrole. Removal of the protecting group provides a phenol which may subsequently be alkylated in the presence of an alkylating agent and base to give an ether or acylated with an isocyanate to give carbamates. Phenols may be converted to aryl ethers by reaction with an aryl bismuthane in the presence of copper II acetate.

Aryl and heteroaryl groups may be attached to pyrrole pendant aryl and heteroaryl groups by application of coupling chemistry technology as outlined above.

- The sequence and conditions of the reaction steps is dependant on the structure and functional groups present. Protecting groups may be necessary and may be chosen with reference to "Protecting Groups in Organic Synthesis", Greene T. W., Wiley-Interscience, New York, 1981". The blocking groups are readily removable, i.e., they can be removed, if desired, by procedures which will not cause cleavage or other disruption of the remaining portions of the molecule. Such procedures include chemical and enzymatic hydrolysis, treatment with chemical reducing or oxidizing agents under mild conditions, treatment with fluoride ion, treatment with a transition metal catalyst and a nucleophile, and catalytic hydrogenation.

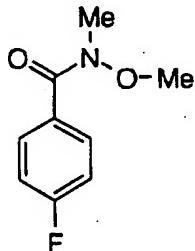
- 60 -

Examples of suitable hydroxyl protecting groups are:
t-butylmethoxyphenylsilyl, t-butoxydiphenylsilyl, trimethylsilyl,
triethylsilyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl,
benzylloxycarbonyl, t-butyloxycarbonyl, 2,2,2-trichloroethoxy-
5 carbonyl, and allyloxycarbonyl. Examples of suitable carboxyl
protecting groups are benzhydryl, o-nitrobenzyl, p-nitrobenzyl,
2-naphthylmethyl, allyl, 2-chloroallyl, benzyl, 2,2,2-trichloroethyl,
trimethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl,
2-(trimethylsilyl)ethyl, phenacyl, p-methoxybenzyl, acetonyl,
10 p-methoxyphenyl, 4-pyridylmethyl and t-butyl.

The following examples are illustrative and are not limiting
of the compounds of this invention.

15 The invention is described in connection with the following
non-limiting examples.

PREPARATIVE EXAMPLE 1

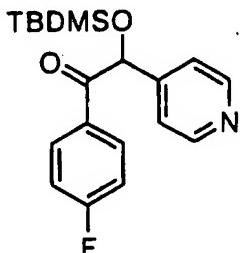


20 To a 2 liter 3 neck flask equipped with a magnetic stirrer
was added 67.7 g of N,O-dimethylhydroxylamine and 750 ml of
CH₂Cl₂ followed by 153 g (1.51 moles) of triethyl amine. The solution
was cooled to 5°C and treated with 100 g of 4-fluorobenzoyl chloride
25 dropwise. The mixture was warmed to room temperature and stirred
over night. The mixture was filtered and the solid was washed with
ether. The organic phase was washed with water (1 x 2 liter) and brine

- 61 -

(1 x 1 liter). The organic phase was dried over MgSO₄, filtered and concentrated in vacuo to give the desired product.

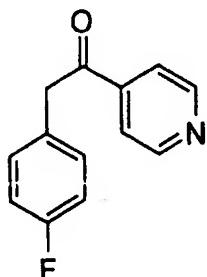
PREPARATIVE EXAMPLE 2



- To a 2 liter 3 neck flask equipped with a mechanical stirrer under N₂ was added 54.6 g (0.59 m) diisopropylethylamine and 150 ml of THF. The solution was cooled to -20°C and treated with 268 ml (0.67 m) of 2.5 M butyl lithium over 20 minutes. To the reaction mixture was added 125 g (0.56 m) of 4-(t-butyldimethylsilyloxy)methyl-pyridine in 100 ml of THF over 30 minutes. The reaction mixture was stirred for 1 hour at -15°C and then treated with a solution of 108 g (0.59 m) of the product of Preparative Example 1 dissolved in 100 ml of THF dropwise. The reaction was warmed to 0°C and stirred for 1 hour and then was warmed to room temperature and was quenched by addition of 1 liter of 20% NH₄Cl solution. The aqueous phase was extracted with EtOAc (3 x 500 ml). The combined organic phases were washed with water (1 x 500 ml), 1 x 500 ml brine and were dried over MgSO₄. The mixture was filtered and the filtrate was concentrated in vacuo to give a dark oil. The product was purified by flash chromatography over silica gel eluting with 10-20% EtOAc/hexanes.

- 62 -

PREPARATIVE EXAMPLE 3

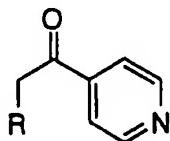


- To a solution of 4-dimethoxymethylpyridine (Synthetic
5 Comm. 23, 1967-1971, 1993) (0.94 g, (6 mmol)) in 10 ml of dry THF
was added at -78°C 4.03 ml of 1.6 M n-butyl lithium in hexanes
dropwise. After 15 minutes 1.2 g (6.4 mmol) of 4-
10 bromomethylfluorobenzene was added dropwise. The reaction mixture
was allowed to gradually warm to room temperature. The mixture was
diluted with 10 ml of water and 50 ml of ethyl acetate. The phases were
separated and the aqueous phase was extracted with ethyl acetate (2 x 10
ml). The combined organic phases were washed with brine and dried
over MgSO₄. The mixture was filtered and the filtrate was
concentrated in vacuo. The residue was dissolved in 20 ml of formic
15 acid, heated to 80°C for 2 hours and then allowed to stand at room
temperature over night. The reaction mixture was concentrated in
vacuo and diluted with 20 ml of EtOAc and washed with saturated
sodium bicarbonate solution. The organic phase was dried over
MgSO₄, filtered and concentrated in vacuo to give the desired product.
20 ¹H NMR (CDCl₃, 300 MHz): 4.25 (s, 2H); 7.02 (t, 2H);
7.19 (dd, 2H); 7.76 (dd, 2H); 8.80 (d, 2H).

PREPARATIVE EXAMPLES 4-10

- 25 The following compounds were prepared using the method
described in Preparative Example 3, with appropriate changes in the
starting material.

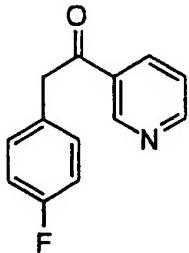
- 63 -



Prep. Example #	R
4	4-Cl-Ph
5	4-CF ₃ -Ph
6	3-Cl-Ph
7	4-MeO-Ph
8	4-Br-Ph
9	3-Br-Ph
10	4-t-Bu-Ph

PREPARATIVE EXAMPLE 11

5



- To 1.0 g (4.8 mmol) of the O-trimethylsilylcyanohydrin of 3-pyridaldehyde (Chem. Ber. 112, 2045, 1979) dissolved in 5 ml of THF at -78°C was added 2.64 ml of 2.0 M lithium diisopropylamide. After 30 minutes 0.91 g (4.8 mmol) of 4-bromomethylfluorobenzene was added and the mixture was stirred as the temperature was permitted to increase to room temperature over 2 hours. 10 ml of 2M HCl solution followed by 5 ml of methanol (MeOH) was added and stirring was continued for 2 hours. The reaction mixture was extracted with 10

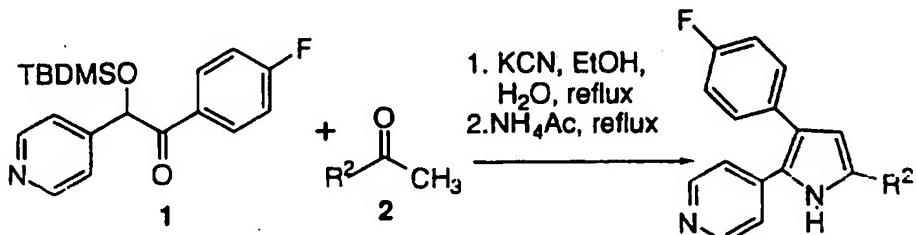
ml of ethyl acetate (EtOAc) (Ac = acetate). The EtOAc phase was extracted with 1N HCl (2 x 10 ml). The combined acidic aqueous phases were extracted with CH₂Cl₂ (3 x 15 ml) and then made basic by addition of 3N NaOH solution. The resulting emulsion was extracted
5 with CH₂Cl₂ (3 x 20 ml). The combined organic extracts were washed with brine (1 20 ml) and dried over MgSO₄ to give the product sufficiently pure for conversion to pyrroles as described below.

FAB m/s: C₁₃H₁₀NOF= 215, Observed: 216 (M⁺+1). H¹
NMR (CDCl₃, 300 MHz): 4.30 (s, 2H); 7.04 (t, 2H); 7.22 (dd, 2H); 7.42
10 (dd, 1H); 8.26 (dt, 1H); 8.78 (dd, 1H); 9.21 (d, 1H).

- 65 -

EXAMPLES 1-23

(Method 1)



5

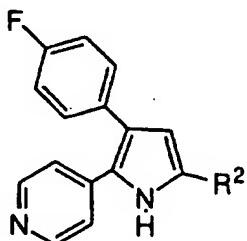
1.0 g (3.9 mmol) of 1, the product of Preparative Example 2, 2.89 mmol of an acetophenone 2, 1.1 mmol of potassium cyanide dissolved in 3.0 ml of ethanol and 0.4 ml of water were refluxed for 2-6 hours. Ammonium acetate (1.5g) was added and the mixture was refluxed for 2-6 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed with saturated sodium bicarbonate and sodium chloride. The organic phase was dried over MgSO₄, filtered and concentrated in vacuo. The products were purified by flash chromatography over silica gel eluting with ethyl acetate and hexane mixtures. The products were characterized by NMR and mass spectrum. ((TBDMS = t-butyl dimethylsilyl)).

10

Using the procedure set forth above and substituting for compound 2, the following compounds were prepared.

15

20

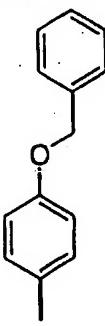
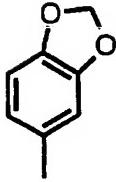


Example #	R ²	FAB ms (M ⁺ +1)
1	4-(MeS)-Ph	361

- 66 -

2	4-(PhO)-Ph	407
3	4-(EtO)-Ph	359
4	4-(c-hex)-Ph	
5	4-(CF ₃)-Ph	383
6	4-Br-Ph	393
7	4-(t-Bu)-Ph	371
8	4-Et-Ph	343
9	4-(PhS)-Ph	423
10	2-Me-Ph	329
11	4-(MeO)-Ph	345
12	4-Me-Ph	329
13	4-Cl-Ph	349
14	4-(n-BuO)-Ph	387
15	4-(BzlO)-Ph	421
16	4-F-Ph	333
17	3,4-di-Cl-Ph	383
18	3-CF ₃ -Ph	383
19	3,4-di-F-Ph	351
20	3,4-(OCH ₂ O)-Ph	359
21	3-Cl-4-F-Ph	367
22	3-Me-4-Cl-Ph	363
23	4-CF ₃ O-Ph	399

Me = methyl c-hex = cyclohexyl t-Bu = t-butyl Ph = phenyl Et = ethyl Bzl = benzyl Cbz = carboxybenzyl 3,4-(OCH₂O)-Ph represents



4-(BzlO)-Ph represents

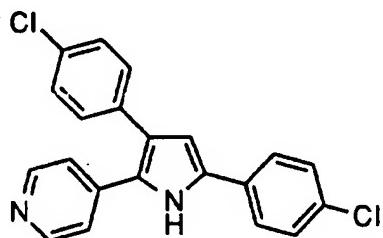
- 67 -

EXAMPLE 24

(Method 2)

3-(4-CHLOROPHENYL)-5-(4-CHLOROPHENYL)-2-(4-PYRIDYL)-
PYRROLE

5



To a solution of 0.083 g (0.36 mmol) of the product of Preparative Example 4 in 1 ml of dry DMSO at room temperature was
10 added 0.4 ml (0.4 mmol) of a 1.0 M solution of sodium hexamethyldisilazide in THF. The solution was stirred for 15 minutes and then treated with a solution of 0.093 g (0.4 mmol) of 4-chlorophenacyl bromide in 0.5 ml of DMSO. The reaction mixture was stirred for 1 hour and then diluted with 10 ml of water and 5 ml of
15 saturated NH₄Cl solution. The mixture was extracted with ethyl acetate (3 x 10 ml) and the organic phases were combined and washed with brine (1 x 10 mL) and dried over MgSO₄. The mixture was filtered and concentrated in vacuo. The residue was dissolved in 2 ml of glacial acetic acid and heated at 110°C in the presence of 1.0 g NH₄OAc for 2
20 hours. The solution was diluted with 10 ml of water and extracted with EtOAc (3 x 10 ml). The combined organic extracts were washed with brine (1 x 10 ml) and dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by rotary chromatography over silica gel eluting with 4% MeOH/CH₂Cl₂ to give the desired product.
25 FAB ms :365 (M⁺⁺1).

EXAMPLES 25-39

Using the procedure set forth in Example 24 (Method 2) and substituting the starting material identified in column two, the compounds of examples 26 - 40 were prepared. If the starting material is not specified, it was prepared as described in the foregoing examples using an appropriate change in the starting compounds.

Ex. #	Starting Mat. Prep. Ex.	R ²	R ⁴	HAr	FAB ms (M ⁺ +1)
25	5	4-Cl-Ph	4-CF ₃ -Ph	4-Pyr	399
26	6	4-Cl-Ph	3-Cl-Ph	4-Pyr	365
27	11	4-Cl-Ph	4-F-Ph	3-Pyr	349
28	7	4-Cl-Ph	4-MeO-Ph	4-Pyr	361
29	3	4-NO ₂ -Ph	4-F-Ph	4-Pyr	360
30	3	3-NO ₂ -Ph	4-F-Ph	4-Pyr	360
31	3	2-NO ₂ -Ph	4-F-Ph	4-Pyr	360
32	3	4-(CO ₂ Et)-Ph	4-F-Ph	4-Pyr	387
33	3	4-CN-Ph	4-F-Ph	4-Pyr	340
34	9	4-Cl-Ph	3-Br-Ph	4-Pyr	411
35	-	4-Cl-Ph	4-(1-naphthyl)-Ph	4-Pyr	457
36	3	3-CN-Ph	4-F-Ph	4-Pyr	340
37	8	4-Cl-Ph	4-Br-Ph	4-Pyr	411
38	10	4-Cl-Ph	4-t-Bu-Ph	4-Pyr	387
39		4-Cl-Ph	2-F-4-Br-Ph	4-Pyr	425

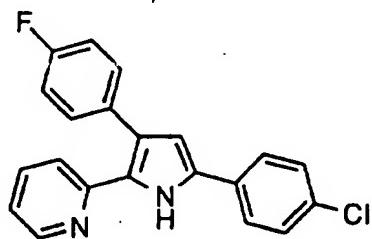
- 69 -

EXAMPLE 40

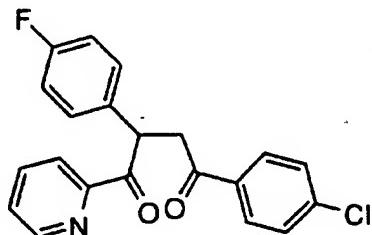
(Method 3)

5-(4-CHLOROPHENYL)-3-(4-FLUOROPHENYL)-2-(2-PYRIDYL)-PYRROLE

5



Step 1



10 A solution of 0.5 g (1.9 mmol) of 4-fluoro-4'-chlorochalcone in 4 ml of dioxane was treated with 47 mg (0.19 mmol) of 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide and 76 mg (0.76 mmol) triethylamine and heated to 70°C. To this mixture was added 0.22 g (2.09 mmol) of 2-pyridaldehyde, drop wise over 1.5 hours. The
15 reaction mixture was heated for 10 hours at 70°C and then cooled to room temperature. 5 ml of ethanol was added and the reaction mixture was concentrated in vacuo. A white precipitate formed that was collected by filtration to give the desired intermediate.

In examples where R² is pyridin-4-yl (and other heteroaryl aldehydes), pyridaldehyde is added to a suspension of 5 mole % NaCN in DMF under N₂. A red solution is formed. To this solution is added the requisite chalcone (in general prepared by condensation of an

- 70 -

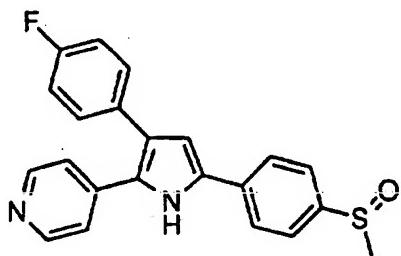
- acetophenone and aldehyde in the presence of NaOH in MeOH). After approximately 4 hours the solution is diluted with EtOAc and washed with water and brine, and dried over MgSO₄. The mixture is filtered and the filtrate is concentrated in vacuo to provide the crude 1,4-diketone. The diketone is purified further by flash chromatography or committed directly to the condensation outlined below.

Step 2

- 10 0.1 g of the product from Step 1 was dissolved in 2 ml of acetic acid and heated at 110°C for 90 minutes with 1.0g of ammonium acetate. The reaction mixture was cooled and diluted with 5 ml of EtOAc, washed with water (2 x 5 ml), brine (1 x 5 ml) and dried over MgSO₄. The mixture was filtered and the filtrate was concentrated in vacuo to give the desired product.
- 15 FAB ms: C₂₁H₁₄N₂ClF = 348, Observed 349 (M⁺⁺1).
¹H NMR (CDCl₃, 300 MHz): 6.55 (d, 1H); 7.02-7.60 (m, 11H); 8.48 (dm, 1H); 10.40 (bs, 1H).

EXAMPLE 41

- 20 5-(4-METHYLSULFINYLPHENYL)-3-(4-FLUOROPHENYL)-2-(4-PYRIDYL)-PYRROLE



- To a solution of 55.5 mg (0.15 mmol) of the product of Example 1 in 2 ml of acetic acid and 1.4 ml of water was added 50.01 mg (0.185 mmol) of potassium persulfate. The reaction mixture was stirred for 1.5 hours. The mixture was diluted with water (5 ml) and neutralized by addition of ammonium hydroxide. The resulting solid

INTERNATIONAL SEARCH REPORT

International application No. PCT/US96/18539

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

The multitude of variables and their permutations and combinations (e.g. HAr, Ra, Rb, R1, R2, R3, R4, R20 etc.) result in claimed subject matter that is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Note also that the claimed subject matter lacks a significant structural element qualifying as the special technical feature that clearly defines a contribution over the art. The subject matter claimed contains a pyrrole ring which does not define a contribution over the prior art. Therefore, the first discernable invention as found in Example 1, (the compound therein, a pharmaceutical composition therewith and a method of treating diabetes therewith) has been searched.

- 71 -

was recovered by filtration and purified by flash chromatography over silica gel eluting with 5% MeOH/CH₂Cl₂ to give the title compound.

FAB ms: C₂₂H₁₇N₂OSF= 376, Observed 377 (M⁺⁺1).

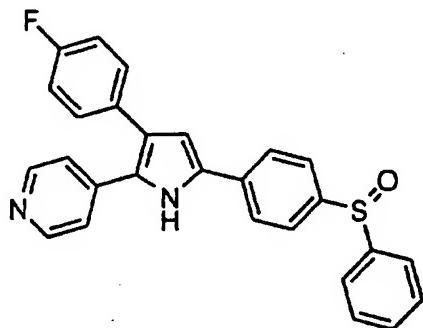
¹H NMR (CDCl₃, 300 MHz): 2.70 (s, 3H); 6.90 (s, 1H); 7.08 (t, 2H);

5 7.23 (d, 2H); 7.35 (dd, 2H); 7.61 (d, 2H); 7.80 (d, 2H); 8.22 (d, 2H).

EXAMPLE 42

3-(4-FLUOROPHENYL)-5-(4-PHENYLSULFINYLPHENYL)-2-(4-PYRIDYL)PYRROLE

10



The procedure set forth in Example 41 was utilized, substituting the product of Example 9 as the starting material.

FAB ms: C₂₂H₁₇N₂OSF= 376, Observed 377 (M⁺⁺1).

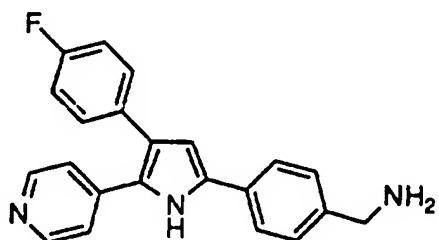
15

- 72 -

EXAMPLE 43

5-(4-AMINOMETHYLPHENYL)-3-(4-FLUOROPHENYL)-2-(4-PYRIDYL)PYRROLE

5



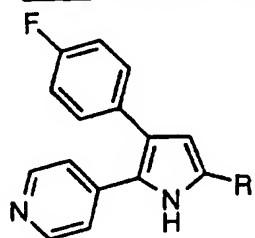
To a solution of 20 mg (0.051 mmol) product of Example 33 dissolved in 2 ml of MeOH was added 0.06 g (0.253 mmol) of cobalt chloride. To this solution was added 0.02 g (0.51 mmol) of sodium borohydride. The mixture was stirred for 1 hour, diluted with EtOAc (5 ml) and washed with water (1 x 10 mL). The aqueous phase was extracted with EtOAc (3 x 10 ml) and the combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by chromatography over LH20 eluting with MeOH to give the desired product.

10 FAB ms: C₂₂H₁₈N₃F = 343, Observed 344 (M⁺⁺).
H¹NMR (CD₃OD, 300 MHz): 4.12 (s, 2H); 6.74 (s, 1H);
7.10 (t, 2H); 7.37 (m, 2H); 7.50 (m, 4H); 7.87 (d, 2H); 8.38 (d, 2H).

15

- 73 -

EXAMPLE 44-46

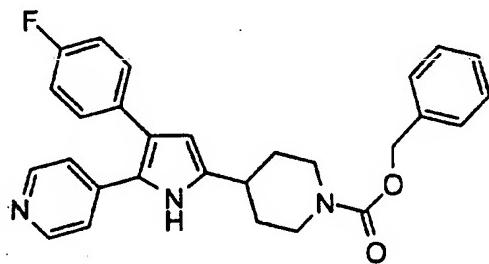


The following compounds are prepared utilizing Method 4,
5 substituting the product of Examples 29-31, respectively, as starting
materials.

Example #	Starting Material	R
44	Example 29	4-NH ₂ -Ph
45	Example 30	3-NH ₂ -Ph
46	Example 31	2-NH ₂ -Ph

10

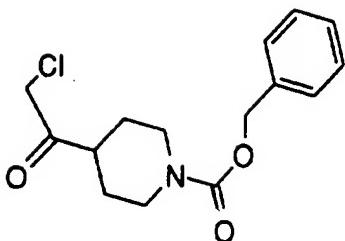
EXAMPLE 47
5-((N-BENZYLOXYCARBONYL)-PIPERIDIN-4-YL)-3-(4-
FLUOROPHENYL)-2-(4-PYRIDYL)-PYRROLE



15

- 74 -

Step 1



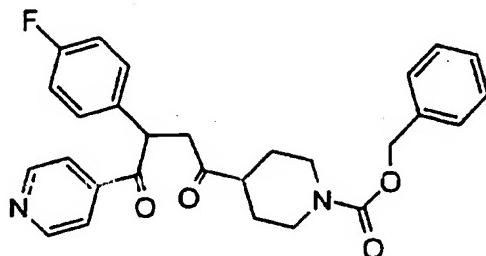
To a solution of N-benzyloxycarbonyl-piperidine-4

- 5 carboxylic acid (5.0 g (19 mmol)) in 20 ml of dry EtOAc at -15°C was added 2.71 g (20.9 mmol) of diisopropylethylamine followed by 2.51 g (20.9 mmol) of isopropenylchloroformate. The reaction mixture was stirred for 1 hour and filtered through a dry sintered funnel into a dry 250 ml round bottom flask at 0°C. The filtrate was treated with ethereal
10 diazo methane (freshly prepared in the normal manner from 10 g of N-methylnitrosourea). The reaction mixture was stirred for 1 hour and then poured into 50 ml of water. The reaction mixture was extracted with ethyl acetate (3x 50 ml). The combined organic phases were washed with brine and dried over Na₂SO₄. The mixture was filtered
15 and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography over silica gel eluting with 50% EtOAc/hexanes to give the intermediate diazomethyl ketone. The material was dissolved in 20 ml of ether and cooled to 0°C and then treated portionwise with 10 ml of 1M HCl in ether. After 1 hour the reaction mixture was poured
20 into 20 ml of saturated NaHCO₃ solution. The product was extracted with EtOAc (3 x 20 ml). The combined organic phases were washed with brine and dried over MgSO₄. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography over silica gel eluting with 30% EtOAc/hexanes to give
25 the desired product.

H¹-NMR (CDCl₃, 300 MHz): 1.56 (m 2H); 1.85 (bm, 2H); 2.87 (m, 3H); 4.12 (s, 2H); 4.20 (bs, 1H); 5.12 (bs, 2H); 7.35 (m, 5H).

- 75 -

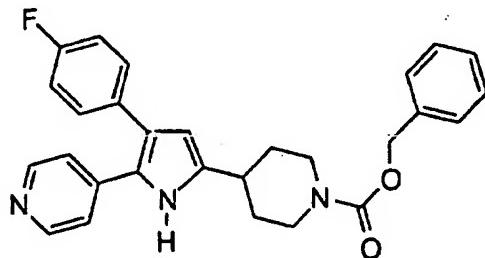
Step 2



5 To a solution of the product of Preparative Example 3 (0.13 g (0.67 mmol)) in 1.5 ml of dry DMSO is added 0.74 ml (0.61 mmol) of a 1M solution of sodium hexamethyl disilazide in THF. After 10 minutes a solution of 0.19 g (0.67 mmol) of the product of Step 1 is added in 1 ml DMSO dropwise. The reaction mixture is stirred for 2 hours, diluted with ethyl acetate (20 ml) and washed with water (3 x 10 ml). The combined organic phases are washed with brine and dried over MgSO₄. The mixture is filtered and the filtrate is concentrated in vacuo. The residue is purified by MPLC over silica gel eluting with 2% MeOH/CH₂Cl₂ to give the desired product.

15

Step 3



20

The product of Step 2 (0.13 g (0.29 mmol)) is heated in 2 ml of acetic acid in the presence of 0.5 g ammonium acetate at 110°C for 2 hours. The reaction mixture is diluted with EtOAc (10 mL) and washed with water. The combined organic phases are washed with

- 76 -

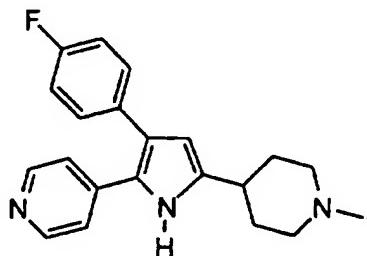
brine and dried over MgSO₄. The mixture is filtered and the filtrate is concentrated in vacuo. The residue is purified by rotary chromatography over silica gel eluting with 5% MeOH/CH₂Cl₂ to give the desired product.

5 FAB ms: 456 (M⁺⁺1).

EXAMPLE 48

5-(N-METHYL PIPERIDIN-4-YL)-3-(4-FLUOROPHENYL)-2-(4-PYRIDYL)PYRROLE

10



A solution of the product of Example 47 in THF at room temperature is treated with 2 equivalents of lithium aluminium hydride. 15 The solution is refluxed for 2 hours, cooled to room temperature and treated with water, extracted with ethyl acetate and dried over sodium sulfate to give the desired product.

FAB ms: 336 (M⁺⁺1).

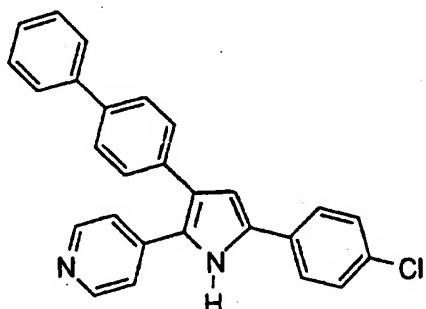
- 77 -

EXAMPLE 49

(Method 4)

5-(4-CHLOROPHENYL)-3-(BIPHENYL)-2-(4-PYRIDYL)PYRROLE

5



To a stirred solution of the bromo compound Example 37 (82 mg, 0.20 mmol) and benzene boronic acid (73 mg, 0.60 mmol) in toluene (5 mL) and EtOH (2.5 mL) was added 1.25 N-NaOH solution (0.82 mL). After the addition of Pd(0)(Ph₃P)₄ (4.6 mg, 0.004 mmol) the solution was degassed by pumping with a vacuum pump three times. The solution was stirred under nitrogen at 90°C for 4 hrs. The product was extracted with EtOAc (3x), the combined organic phase was washed with brine and dried over anhydrous MgSO₄.

Concentration was followed by flash chromatography (H:E = 1:1, 100 % EtOAc) to give the desired product as a slightly yellow solid.

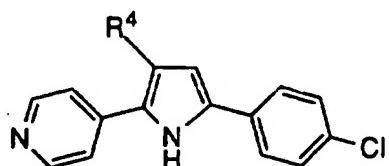
FAB ms: 407 (M⁺+1).

- 78 -

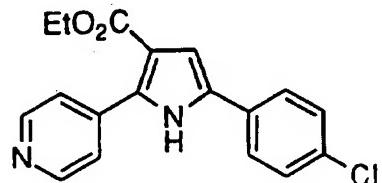
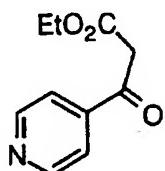
EXAMPLES 50-61

Using the method disclosed in Example 49, the following compounds were prepared using the compounds disclosed in Examples 37 and 34 as starting materials.

5



Example #	R ⁴	Mass Spec. (M ⁺⁺ 1)
50	3-Ph-Ph-	407
51	4-(4-MeO-Ph)-Ph-	437
52	3-(4-MeO-Ph)-Ph-	437
53	4-(4-CF ₃ -Ph)-Ph-	475
54	4-(4-F-Ph)-Ph-	425
55	4-(3-NO ₂ -Ph)-Ph-	452
56	3-(3-NO ₂ -Ph)-Ph-	452
57	4-(4-Me-Ph)-Ph-	421
58	4-(2-thiophenyl)-Ph-	413
59	4-(3-thiophenyl)-Ph-	413
60	3-(2-thiophenyl)-Ph-	413
61	3-(3-thiophenyl)-Ph-	413

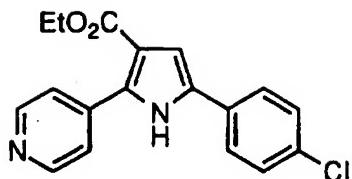
EXAMPLE 625 Step 1Ethyl 3-(4-pyridyl)-3-oxo-propionate

To a solution of 3.02 g of ethyl isonicotinoate in 10 ml of
 10 ethyl acetate under nitrogen was added 0.53 g (0.022 m) of 60% sodium
 hydride portionwise. The reaction mixture was heated to reflux for 3
 hours, cooled and carefully diluted with 20 ml of water and was acidified
 with 5% citric acid solution. The aqueous phase was extracted with
 ethyl acetate. The organic extracts were washed with brine and dried
 15 over MgSO₄, filtered and concentrated in vacuo to give the crude
 product. The material was recrystallized from isopropanol to give the
 desired product.

¹H-NMR (CDCl₃, 300 MHz): keto form: 1.33 (t, 3H); 4.27
 (q, 2H); 5.75 (s, 2H), 7.61 (dd, 2H); 8.72 (dd, 2H). enol form: 1.25 (t,
 20 3H); 4.21 (q, 2H); 7.26 (s, 1H), 7.72 (dd, 2H); 8.83 (dd, 2H).

- 80 -

Step 2

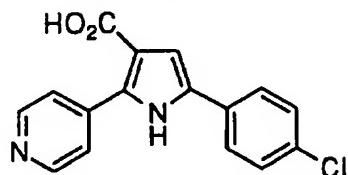


- 5 To a solution of 2.29 g (0.01 m) of the product of Step 1 in 75 ml of ethanol was added at 0°C 4.14 ml (0.011 m) of a 21% wt solution of sodium ethoxide in ethanol. After 10 minutes 2.56 g (0.011 m) of 4-chloro-bromoacetophenone in ethanol was added. The reaction mixture was warmed to room temperature for 30 minutes and then
10 heated at 70°C for 2 hours. The mixture was allowed to age overnight at room temperature. The reaction mixture was acidified with 5% citric acid and diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine and dried over MgSO_4 , filtered and concentrated in vacuo to give the crude 1,4 diketone
15 intermediate. The material was dissolved in 50 ml of acetic acid and heated with 5 grams of ammonium acetate until the starting material had been consumed. The reaction mixture was diluted with ethyl acetate, washed with water and dried by washing with brine and standing over MgSO_4 . The mixture was filtered and the filtrate was concentrated in
20 vacuo. The crude product was purified by flash chromatography eluting with 5% MeOH/ CH_2Cl_2 .

$^1\text{H-NMR}$ (CD_3OD , 300 MHz): 1.20 (t, 3H); 4.15 (q, 2H); 6.98 (s, 1H); 7.31 (d, 2H); 7.60 (d, 2H); 7.82 (bd, 2H); 8.50 (bs, 2H).

- 81 -

EXAMPLE 63

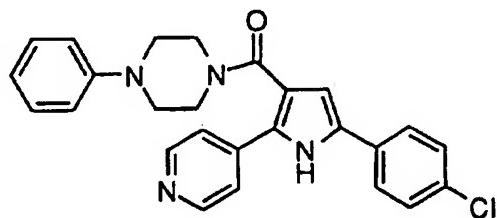


- To a suspension of 1.85 g (5.67 mm) of the product of
 5 Example 62 in 25 ml of ethanol was added 25 ml of a 5% lithium
 hydroxide solution. The solution was heated at reflux for 5 hours. The
 conversion of the starting material (rf 0.3 in 5% MeOH/CH₂Cl₂) to
 product (rf 0.05 in 5% MeOH/CH₂Cl₂) was monitored by TLC. The
 reaction mixture was diluted with water, filtered and acidified to give
 10 the desired acid.

¹⁵ ^H-NMR (CD₃OD, 300 MHz): 7.04 (s, 1H); 7.41 (d, 2H);
 7.68 (d, 2H); 7.77 (d, 2H); 8.55 (bd, 2H).

EXAMPLE 64

15



- A solution of 0.05 g (0.16 mmol) of the product of
 Example 63 in 1 ml of DMF 0.025 g (0.16 mmol) of N-phenyl
 20 piperazine, 0.026 ml (0.25 mmol) of N-methyl morpholine, 0.032 g
 (0.24 mmol) of N-hydroxybenzotriazole and 0.045 g (0.24 mmol) of 1-
 ethyl-3-(3-dimethylaminopropyl)carbodiimide. The solution was stirred
 at room temperature over night and diluted with water. The aqueous
 phase was extracted with ethyl acetate. The organic phase was dried
 25 over MgSO₄, filtered and concentrated in vacuo. The residue was

purified by rotory chromatography eluting with 4% MeOH/CH₂Cl₂ to provide the desired product.

FAB ms: C₂₆H₂₃N₄ClO, calc=442; observed 443 (M⁺⁺1).

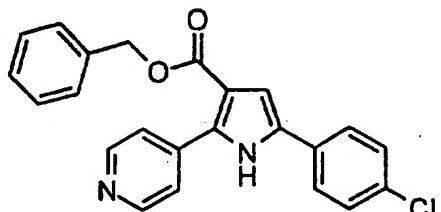
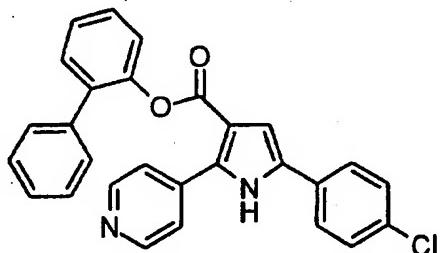
5

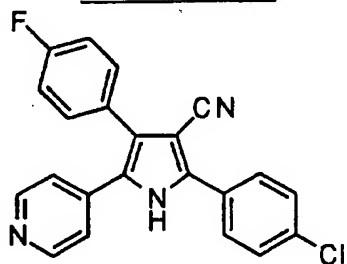
EXAMPLES 65-69

The compounds in the following table were prepared utilizing the procedure disclosed in Example 64.

Example	Compound	Notes/Mass Spec
65		FAB ms: C ₂₈ H ₂₇ N ₄ ClO, calc=470; observed 471 (M ⁺⁺ 1)
66		FAB ms: C ₂₈ H ₂₀ N ₃ ClO, calc=449; observed 450 (M ⁺⁺ 1)
67		FAB ms: C ₂₆ H ₂₆ N ₃ ClO, calc=431; observed 432 (M ⁺⁺ 1)

- 83 -

68		Coupling as above with benzyl alcohol, EDC and DMAP. FAB ms: C ₂₃ H ₁₇ N ₂ ClO ₂ , calc=388; observed 389 (M ⁺⁺¹)
69		Coupling as above with 2-phenylphenyl, EDC and DMAP. FAB ms: C ₂₈ H ₁₉ N ₂ ClO ₂ , calc=450; observed 451 (M ⁺⁺¹)

EXAMPLE 70

5

Step 1

To a solution of 1.0 g (4.65 mmol) of Preparative Example 3 in 48% aqueous HBr was added bromine (0.89 g, 5.58 mmol) at room temperature. The reaction mixture was heated to 100°C for 1 hour and then cooled to room temperature and allowed to stand 5 overnight. The resulting yellow precipitate was filtered, washed with acetone and dried in vacuo to provide the bromide.

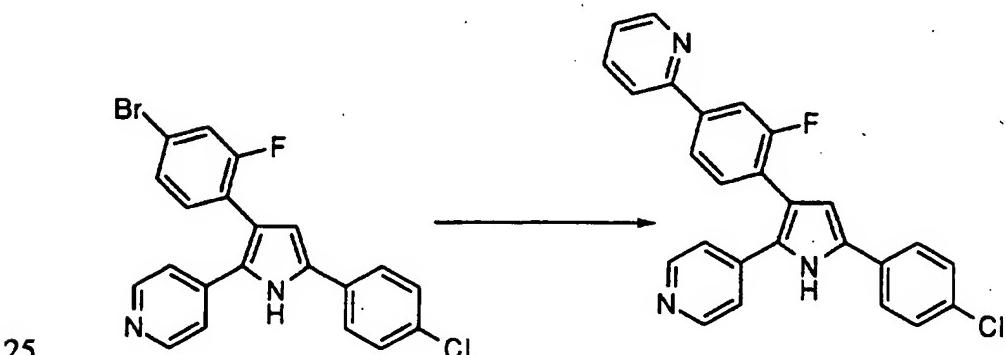
Step 2

- To a solution of 100 mg (0.27 mmol) of the product of Step 10 1 in 3 ml of DMF was added triethylamine. To this mixture was added a solution of the preformed sodium salt of 2-cyano-4'-chloroacetophenone (57.5 mg, 0.32 mmol). The reaction mixture was stirred at room temperature for 1 hour, concentrated in vacuo and was partitioned between EtOAc and water. The aqueous phase was extracted with 15 EtOAc. The combined organic phases were washed with brine, dried over MgSO₄ filtered and concentrated in vacuo. The residue was committed to the condensation with ammonium acetate as described previously to provide the desired product following purification by flash chromatography.

20

EXAMPLE 71

(Method 4a-1)

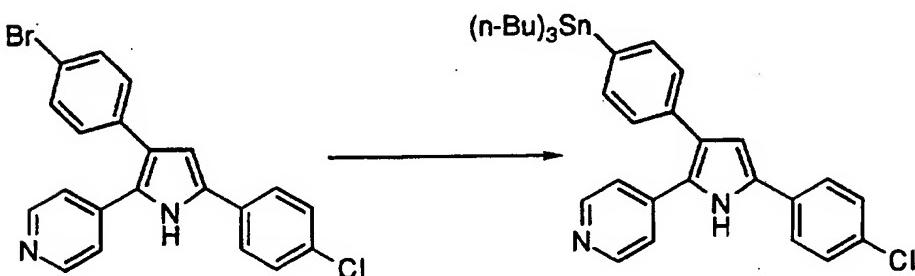


- 85 -

- A solution of the compound of Example 39 in toluene was treated with 2 equivalents of 2-tributylstannylyl pyridine and 5 mole % of tetrakistriphenylphosphine. The solution was heated to 100°C and monitored by TLC for consumption of starting material. The reaction mixture was concentrated in vacuo and was purified by flash chromatography over silica gel eluting with an appropriate solvent to provide the desired product.
- 5 FAB ms: C₂₆H₁₇N₃Cl₁₁F₁ calc=425 observed 426 (M⁺⁺1).

10

EXAMPLE 72
(Method 4a-2)

15 Step 1

A solution of the compound of Example 37 in dioxane was heated with hexabutylditin in the presence of 5 mole % tetrakistriphenylphosphine at 80°C until the starting material had been consumed as determined by TLC. The reaction mixture was

- 20 concentrated in vacuo and purified by flash chromatography over silica gel eluting with 1:1 EtOAc/hexanes to provide the desired intermediate.
¹H-NMR (CDCl₃-400 MHz): 0.31 (s, 9H); 6.64 (dd, 1H); 7.26 (m, 2H); 7.36 (t, 4H); 7.50 (t, 4H); 8.49 (dd, 2H); 8.65 (bs, 1H).

25 Step 2

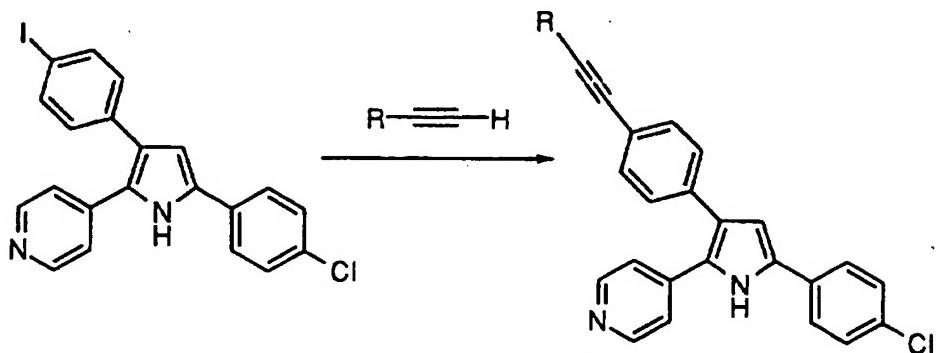
The product of Step 1 was combined with 3 equivalents of the requisite anhydride, and 5 mole % tetrakistriphenylphosphine in toluene at 100°C, and was heated until the starting material had been consumed. The reaction mixture was concentrated in vacuo and

- 86 -

purified by flash chromatography over silica gel eluting to provide the desired product.

5

EXAMPLE 73-81
(Method 5)

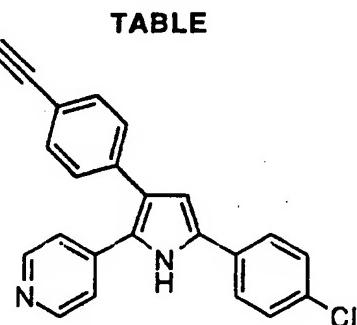


A solution of 3-(4-iodophenyl)-5-(4-chlorophenyl)-2-(4-pyridyl)pyrrole, prepared via method 2, in piperidine was treated with 2-3 equivalents of an acetylene, 5 mole % tetrakis(triphenylphosphine), 5
10 mole % cuprous iodide and 5 mole % triphenylphosphine. The reaction mixture was degassed and then heated at 100°C for 4.5 hours. The reaction mixture was concentrated in vacuo and was purified by flash chromatography over silica gel eluting with an appropriate solvent to provide the desired product.

15 The following compounds were prepared by the methods described above.

- 87 -

TABLE

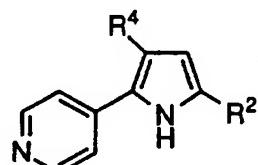


Expl. No.	R	FAB ms	Method
73	H	355	4b*
74	phenyl	431	5
75	n-butyl	411	5
76	4-methyl-phenyl	445	5
77	4-Cl-phenyl	465	5
78	2-pyridyl	432	5
79	4-F-phenyl	449	5
80	4-ethylphenyl	459	5
81	4-butylphenyl	487	5

* Coupled with trimethylsilyl acetylene followed by treatment with tetrabutyl ammonium fluoride.

EXAMPLES 82-289

The following compounds were prepared using the procedures described above.

TABLE

Expl. No.	R ²	R ⁴	FAB ms	Method	Ntes
82	4-(COOH)-Ph	4-F-Ph	358.1	6	1
83	4-Cl-Ph	4-(3-(i-Bu)-6-(SO ₂ NH-t-Bu)-phenyl)-Ph	598	4	
84	4-Cl-Ph	4-(4-(n-Bu)-phenyl)-Ph	463	4	
85	4-Cl-Ph	4-(3-(iBu)-6-(SO ₂ NH ₂)-phenyl)-Ph	542	6	2
86	4-Cl-Ph	3-(4-(n-Bu)-phenyl)-Ph	463	4	
87	4-Cl-Ph	4-(5-(n-Bu)-thiophenyl)-Ph	469	4	
88	4-Cl-Ph	2-(F)-4-(5-(n-Bu)-thiophen-2-yl)-Ph	487	4	
89	4-Cl-Ph	3,5-di-Br-Ph	475	3	
90	4-Cl-Ph	3,5-(thiophen-2-yl)-Ph	495	4	
91	4-Cl-Ph	3,4-di-(4-OMe-Ph)-Ph	543	4	
92	4-Cl-Ph	3,5-di-(4-Me-Ph)-Ph	511	4	
93	4-Cl-Ph	4-(OCH ₂ CO ₂ Me)-Ph	419.3	3	
94	4-Cl-Ph	4-OMe-Ph	375.1	3	
95	4-Cl-Ph	4-i-Pr-Ph	373.2	3	

96	4-Cl-Ph	4-OBzI-Ph	437.1	3	
97	4-Cl-Ph	5-Ph-thiazol-2-yl	414.2	3	
98	4-Cl-Ph	4-Br-thiophen-2-yl	417.1	3	
99	4-Cl-Ph	2-OPr-Ph	389.2	3	
100	4-Cl-Ph	3-thiophenyl	337.1	3	
101	4-Cl-Ph	3,5-di-(3-nitrophenyl)-Ph	573	4	
102	4-Cl-Ph	4-(benzofuran-2-yl)-phenyl	447	4	
103	4-Cl-Ph	3-Br-5-(thiophen-2-yl)-Ph	493	4	
104	4-Cl-Ph	4-(5-Cl-thiophen-2-yl)-Ph	447	4	
105	4-Cl-Ph	4-(3,5-di-CF ₃ -Ph)-Ph	543	4	
106	4-Cl-Ph	4-(2-OMe-Ph)-Ph	437	4	
107	4-Cl-Ph	4-(4-Cl-Ph)-Ph	441	4	
108	4-Cl-Ph	4-(CO ₂ Me)-Ph	389	2	
109	4-Cl-Ph	2-F-4-(thiophen-2-yl)-Ph	431	4	
110	4-Cl-Ph	4-(3-(NH ₂)-Ph)-Ph	422	4	
111	4-Cl-Ph	4-(3-(OMe)-Ph)-Ph	437	4	
112	4-Cl-Ph	2-Br-Ph	411	2	
113	4-Cl-Ph	2,6-di-F-Ph	367	2	
114	4-Cl-Ph	3-OBnZl-Ph	437.1	3	
115	4-Cl-Ph	4-(<i>trans</i> -ethenyl-Ph)-Ph	433.1	3	
116	4-Cl-Ph	9-phenanthrenyl	431.1	3	
117	4-Cl-Ph	3-(OPh)-Ph	423.0	3	
118	4-Cl-Ph	2-(OMe)-Ph	361.1	3	
119	2,4-di-Cl-Ph	4-F-Ph	383.0	2	
120	t-Bu	4-F-Ph	295.2	2	
121	Me	4-F-Ph	253.1	2	

- 90 -

122	4-Cl-Ph	4-CN-Ph	356	3	
123	4-Cl-Ph	2,4-di-F-Ph	367	2	
124	4-Cl-Ph	2,4,6-tri-F-Ph	385	2	
125	4-Cl-Ph	2-(3-OMe-Ph)-Ph	437	4	
126	4-Cl-Ph	2-(3-NO ₂ -Ph)-Ph	452	4	
127	4-Cl-Ph	2-thiophen-2-yl-Ph	413	4	
128	4-Cl-Ph	2-indolyl	370.1	3	
129	4-Cl-Ph	2-OEt-Ph	375.1	3	
130	4-Cl-Ph	2-OH-5-Br-Ph	425.7	3	
131	4-Cl-Ph	2-OMe-5-Br-Ph	441.0	3	
132	4-Cl-Ph	5-(2-(CO ₂ Me)-thiophen-3-yl)-furan-2-yl	461.1	3	
133	4-Cl-Ph	2,5-di-OMe-Ph	391.1	3	
134	3-Cl-Ph	4-F-Ph	349.1	2	
135	4-F-Ph	4-F-Ph	393.0	3	
136	4-Cl-Ph	4-(tetrazol-5-yl)-Ph	399	6	a
137	4-F-Ph	4-(thiophen-2-yl)-Ph	397.0	5	
138	2-F-Ph	4-F-Ph	333.1	2	
139	4-Cl-Ph	2-F-4-(2-(5-Cl-thiophen-2-yl)-Ph)	465	4	
140	4-Cl-Ph	4-(CONH-t-Bu)-Ph	430	6	3
141	2-OMe-4-Cl-Ph	4-F-Ph	379.1	2	
142	4-Cl-Ph	4-(N-methyltetrazolyl)-Ph	413	6	b
143	4-Cl-Ph	2-Cl-4-Br-Ph	444	3	
144	4-Cl-Ph	4-(CO ₂ Et)-Ph	403	3	
145	4-N-acetyl-piperidinyl	4-F-Ph	364.1	6	4

- 91 -

146	4-N-(methoxycarbonyl)-piperidinyl	4-F-Ph	380.1	6	5
147	4-N-(isopropoxycarbonyl)-piperidinyl	4-F-Ph	408.1	6	5
148	4-piperidinyl	4-F-Ph	322.1	6	6
149	4-Cl-Ph	2-ethoxy-5-Br-Ph	453.0	3	
150	4-Cl-Ph	2,5-di-F-Ph	367.0	3	
151	4-Cl-Ph	2-(3-Cl-propoxy)-Ph	423.0	3	
152	4-Cl-Ph	2-propoxy-5-Br-Ph	469.0	3	
153	4-Cl-Ph	2-F-5-Br-Ph	429.0	3	
154	4-Cl-Ph	4-C(O)N(Bzl) ₂ -Ph	554	6	3
155	4-Cl-Ph	4-(3-Pyr)-Ph	408	4	
156	4-Cl-Ph	4-(C(O)-(N-Boc-piperazinyl))-Ph	543	6	3
157	4-Cl-Ph	4-(C(O)NPh ₂)-Ph	514	6	3
158	4-Cl-Ph	4-(C(O)-morpholinyl)-Ph	444	6	3
159	4-Cl-Ph	4-(C(O)-L-proline-O-(t-Bu))-Ph	528	6	3
160	4-Cl-Ph	4-C(O)-spiroindene)-phenyl	542	6	3
161	4-Cl-Ph	4-(5-Me-1,3,4-oxadiazol-2-yl)-Ph	413	6	7
162	4-Cl-Ph	4-(5-(n-Bu)-1,3,4-oxadiazol-2-yl)-Ph	455	6	8
163	4-Cl-Ph	trans-ethenyl-Ph	357.0	3	

- 92 -

164	4-Cl-Ph	2-(t-CHCH-Ph)- Ph	433.0	3	
165	4-Cl-Ph	2-(OBzI)-Ph	437.0	3	
166	4-Cl-Ph	2-(O-(n-hexyl))- Ph	431.1	3	
167	4-Cl-Ph	2-(O-(n-nonyl))- Ph	473.1	3	
168	4-Cl-Ph	2-(O-iPr)-Ph	389.2	3	
169	4-Cl-Ph	2-(O-iBu)-Ph	403.2	3	
170	4-Cl-Ph	2-(O-(n-butyl))- Ph	403.2	3	
171	4-Cl-Ph	2-(O-allyl)-Ph	387.1	3	
172	4-Cl-Ph	2-(OCH ₂ -(2,6-di- Cl-Ph))-Ph	504.9	3	
173	4-Cl-Ph	4-(2-pyr)-Ph	408	4	
174	4-Cl-Ph	4-(2-(SO ₂ NH-(t- Bu))-Ph)-2-F-Ph	560	4	
175	4-Cl-Ph	4-NO ₂ -Ph	376	3	
176	c-hexyl	4-F-Ph	321.1	2	
177	N-(CBzI)- piperidin-4-yl	CO ₂ Et	434.1	2	
178	4-Cl-Ph	4-NH ₂ -Ph	346	6	9
179	4-Cl-Ph	4-(NHCO ₂ -(n- butyl))-Ph	446	6	10
180	4-Cl-Ph	4-(NHSO ₂ -(n- butyl))-Ph	466	6	10
181	4-Cl-Ph	4-(NHSO ₂ - thiophen-2-yl)- Ph	492	6	10
182	4-Cl-Ph	2-(OC(O)- propyl)-Ph	417.1	3	
183	4-Cl-Ph	2- (O(CH ₂) ₃ SMe)- Ph	447.2	3	
184	4-Cl-Ph	4-(NHCO ₂ BzI)- Ph	481	6	10
185	4-Cl-Ph	4-(NHCO ₂ Ph)- Ph	466	6	10

- 93 -

186	N-(COOCH ₂ Ph-4-Cl)-piperidin-4-yl	4-F-Ph	490.2	6	5
187	N-(COOCH ₂ Ph-4-Br)-piperidin-4-yl	4-F-Ph	536.1	6	5
188	N-(COOCH ₂ Ph-4-Ph)-piperidin-4-yl	4-F-Ph	532.3	6	5
189	N-(COOCH ₂ Ph-4-NO ₂)-piperidin-4-yl	4-F-Ph	501.2	6	5
190	N-(COOCH ₂ Ph-3-Cl)-piperidin-4-yl	4-F-Ph	490.2	6	5
191	N-(COOCH ₂ Ph-2,4,5-tri-OMe)-piperidin-4-yl	4-F-Ph	561.3	6	5
192	N-(COOCH ₂ Ph-2-Cl)-piperidin-4-yl	4-F-Ph	490.2	6	5
193	4-NHCO ₂ Bzl-cyclohexyl	4-F-Ph	470.2	2	
194	N-(COOCH ₂ Ph)-piperidin-3-yl	4-F-Ph	456.2	2	
195	4-NH ₂ -cyclohexyl	4-F-Ph	336.1	6	11
196	piperidin-3-yl	4-F-Ph	322.3	6	12
197	4-Cl-Ph	2-OH-Ph	347.2	3	
198	4-Cl-Ph	2-(4-Cl-SPh)-Ph	473.0	3	

199	4-Cl-Ph	2-OPh-Ph	423.1	3	
200	4-Cl-Ph	2-(O(CH ₂) ₃ OMe)-Ph	419.2	3	
201	4-Cl-Ph	2-(OCONMe ₂)-Ph	418.2	3	
202	4-Cl-Ph	2-(S-t-Bu)-Ph	419.1	3	
203	4-Cl-Ph	4-(O(n-Pr))-Ph	389.8	3	
204	4-Cl-Ph	2-(O(n-Pr))-4-(Br)-Ph	469.1	3	
205	4-Cl-Ph	4-(5-((CH ₂) ₄ OH)-thiophen-2-yl)-Ph	485	6	13
206	4-Cl-Ph	4-(5-((CH ₂) ₄ azido)-thiophen-2-yl)-Ph	510	6	14
207	4-Cl-Ph	4-(3-OMe-Ph)-2-(O(n-Pr))-Ph	495.2	4	
208	4-Cl-Ph	3-(O(n-Pr))-Ph	389.2	3	
209	4-Cl-Ph	4-(3-NH ₂ -Ph)-2-(O(n-Pr))-Ph	480.2	3	
210	4-Cl-Ph	benzyl	345	2	
211	4-Cl-Ph	2-(furan-2-yl)-Ph	397	4a-1	
212	4-Cl-Ph	4-(furan-2-yl)-Ph	397	4a-1	
213	4-Cl-Ph	4-(2-OH-5-Br-Ph)-2-(O(n-Pr))-Ph	561.2	4	
214	4-Cl-Ph	4-(5-((n-Bu))-thiophen-2-yl)-2-(O(n-Pr))-Ph	527.3	4	
215	4-Cl-Ph	4-(3-(O(n-Bu))-Ph)-Ph	479	4a-2	
216	4-Cl-Ph	4-(5-((CH ₂) ₄ amino)-thiophen-2-yl)-Ph	484	6-1c	15

- 95 -

217	4-Cl-Ph	4-((n-Bu))-thiophen-2-yl)-Ph	469	4	
218	4-Cl-Ph	1-naphthyl	381.1	3	
219	4-Cl-Ph	quinolin-8-yl	582.1	3	
220	4-Cl-Ph	4-(2-(OMe)-5-Br-Ph)-2-(O(n-Pr))-Ph	575.1	4	
221	4-Cl-Ph	4-(cyclohexyl)-Ph	413	3	
222	4-Cl-Ph	4-(n-Bu)-Ph	387	3	
223	4-Cl-Ph	4-(5-(NO ₂)-thiophen-2-yl)-Ph	458	4a-2	
224	4-Cl-Ph	4-(3-(Me)-thiophen-2-yl)-Ph	427	4a-2	
225	4-Cl-Ph	4-(2,5-di-OMe-Ph)-Ph	467	4a-2	
226	4-Cl-Ph	4-(2,4,6-tri-Me-Ph)-Ph	449	4	
227	4-Cl-Ph	4-(5-ethyl-thiophen-2-yl)-Ph	441	4	
228	4-Cl-Ph	4-(5-Me-thiophen-2-yl)-Ph	427	4a-2	
229	4-Cl-Ph	4-(5-(n-Pr)-thiophen-2-yl)-Ph	455	4	
230	4-Cl-Ph	4-(4-(n-Pr)-Ph)-Ph	449	4a-2	
231	4-Cl-Ph	4-I-Ph	457	2	
232	4-Cl-Ph	4-(5-OMe-pyridin-2-yl)-Ph	438	4	
233	4-Cl-Ph	4-(3-Me-Ph)-Ph	421	4a-2	
234	4-Cl-Ph	4-(3,4-(methylenedioxy)-Ph)-Ph	451	4	

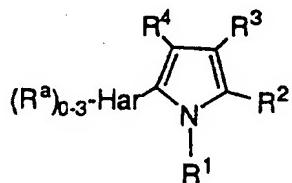
- 96 -

235	4-Cl-Ph	4-(3-(propoxy)-Ph)-Ph	465	4a-2	
236	4-Cl-Ph	4-(3-acetyl-Ph)-Ph	449	4a-2	
237	4-Cl-Ph	4-(3-NO ₂ -4-Me-Ph)-Ph	466	4a-2	
238	4-Cl-Ph	4-(3,4-di-OMe-Ph)-Ph	467	4a-2	
239	4-Cl-Ph	4-(3-(OCH ₂ CH ₂ OMe)-Ph)-Ph	481	4a-2	
240	4-Cl-Ph	4-(4-CN-3-Me-Ph)-Ph	446	4a-2	
241	4-Cl-Ph	4-(5-acetyl-thiophen-2-yl)-Ph	455	4a-2	
242	4-Cl-Ph	CH ₂ CH ₂ -Ph	359.2	3	
243	4-Cl-Ph	CH ₂ CH(Me)-Ph	373.2	3	
244	4-Cl-Ph	CH(Me)CH ₂ -(3,4-(methylenedioxy)-Ph)	417.2	3	
245	4-Cl-Ph	4-(3-(OCH ₂ CH ₂ OEt)-Ph)-Ph	495	4a-2	
246	4-Cl-Ph	4-(indan-1-on-5-yl)-Ph	461	4a-2	
247	4-Cl-Ph	4-(4-Et-Ph)-Ph	435	4	
248	4-Cl-Ph	4-(5-CO ₂ E _t -furan-2-yl)-Ph	469	4a-2	
249	4-Cl-Ph	4-(2-ethyl-phenyl)-Ph	435	4a-2	
250	4-Cl-Ph	2,4-di-propoxy-Ph	447.1	3	
251	4-Cl-Ph	2-propoxy-5-F-Ph	407.1	3	
252	4-Cl-Ph	3,5-di-Br-2-propoxy-Ph	547.0	3	

- 97 -

253	4-Cl-Ph	2-propoxy-5-Cl- Ph	423.1	3	
254	4-Cl-Ph	2-propoxy-3-Cl- Ph	423.0	3	
255	4-Cl-Ph	2-propoxy-3-F- Ph	507.1	3	
256	4-Cl-Ph	4-(5- pyrimidinyl)-Ph	409	4a-2	
257	4-Cl-Ph	cyclohexyl	357	3	
258	2-Br-Ph	4-F-Ph	393	3	

1. By hydrolysis of the compound of Example 32.
2. Treated the compound of Example 83 with TFA/CH₂Cl₂.
3. Saponification of the compound of Example 108 followed by EDC coupling with an amine.
4. EDC coupling of acetic acid with the compound of Example 148.
5. Acylation of the compound of Example 148.
6. Reduction of the compound of Example 47 with H₂, 10% Pd/C.
7. Example 144 refluxed with excess NH₂NH₂, for 1 hr, concentrated in vacuo, heated with trimethyl orthoacetate at 120°C for 17 hrs.
8. Example 144 refluxed with excess NH₂NH₂, for 1 hr, concentrated in vacuo, heated with triethyl orthobutyrate at 120°C for 17 hrs.
9. Example 175, H₂, 10%Pd/C.
10. Acylation or sulphonylation of the compound of Example 178.
11. Catalytic hydrogenation of Example 193.
12. Catalytic hydrogenation of Example 194.
13. Following Stille coupling of Example 37 followed by treatment with tetrabutyl ammonium fluoride in THF.
14. Treatment of Example 205 with mesyl chloride, pyridine, 0°C, followed by NaN₃, DMF, 25°C, 17 hrs.
15. Example 206, triphenylphosphine, H₂O.
 - a Treatment of Example 122 with Me₃SnN₃.
 - b Treatment of Example 136 with MeI and Et₃N.



Ex.	R ¹	(R ^a) ₀₋₃ -Har	R ⁴	R ³	R ²	FAB ms	Method	Nts
259	H	3-Pyr	4-F-Ph	H	4-Cl-Phenyl	349	2	
260	H	2-furoyl	4-Pyr	H	Phenyl	287.2	3	
261	H	2-Pyr	4-Pyr	H	Phenyl	298.2	3	
262	H	3-quinolinyl	4-Pyr	H	Phenyl	348.0	3	
263	H	3-Pyr	4-Pyr	H	Phenyl	298.1	3	
264	H	4-Pyr	4-F-Ph	Br	4-Cl-Phenyl	429.0	3	
265	H	4-Pyr	4-F-Ph	Cl	4-Cl-Ph	383.1	3	
266	H	4-quinolinyl	4-F-Ph	H	4-Cl-Ph	399	3	
267	H	4-(2-F)-pyr	4-F-Ph	H	4-Cl-Ph	367	3	
268	H	3-F-4-pyr	4-F-Ph	H	4-Cl-Ph	367	3	
269	H	3-(Me)-4-pyridyl	4-F-Ph	H	4-Cl-Ph	363	3	
270	H	4-(2-Me)-pyridyl	4-F-Ph	H	4-Cl-Ph	363	3	
271	2-OH-Ph	4-pyr	2-F-4-Br-Ph	H	4-Cl-Ph	520	2	
272	H	4-pyr	4-F-Ph	Me	4-Cl-Ph	363	2	
273	H	4-Pyr	4-F-Ph	Et	4-Cl-Ph	377	2	
274	H	4-Pyr	4-F-Ph	Ph	4-Cl-Ph	425	2	
275	H	2-NH ₂ -pyridin-4-yl	4-F-Ph	H	4-Cl-Ph	364.1	6	a
276	H	pyrimidin-4-yl	4-F-Ph	H	4-Cl-Ph	350.1	3	
277	H	quinolin-6-yl	4-F-Ph	H	4-Cl-Ph	399	3	

- 100 -

278	H	2-F-pyridin-5-yl	4-F-Ph	H	4-Cl-Ph	367.1	3	
279	H	4-Pyr	3-CF ₃ -Ph	Me	N-methyl-piperidin-4-yl	374	2	
280	H	4-Pyr	3-CF ₃ -Ph	Me	piperidin-4-yl	388	2	
281	H	2-OH-pyridin-5-yl	4-F-Ph	H	4-Cl-Ph	365	6	b
282	H	pyridazin-4-yl	4-F-Ph	H	4-Cl-Ph	350	3	
283	H	4-Pyr	4-F-Ph	H	2-CN-Ph	340	6	d
284	H	4-Pyr	2-CN-Ph	H	4-Cl-Ph	356	6	e
285	H	4-Pyr	4-F-Ph	n-Bu	4-Cl-Ph	405	2	
286	H	4-Pyr	2-propoxy-4-(2-Ph ethynyl)-Ph	H	4-Cl-Ph	490	5	c
287	H	4-Pyr	4-(2-propenyl)-cyclohexen-1-yl	H	4-Cl-Ph	375	3	
288	H	4-Pyr	N-(Cbz)-piperidin-4-yl	H	4-Cl-Ph	472	3	
289	H	4-Pyr	i-Propyl	H	4-Cl-Ph	297	3	

a Part a: Example 267, MeOPhCH₂NH₂, 150°C. Part b: TFA/CH₂Cl₂

b Heating compound no. 278 in acetic acid at 100°C.

c Coupling of compound 204 with phenylacetylene.

d Coupling of compound 258 with ZnCN₂ and Pd(PPh₃)₄.

e Coupling of compound 112 with ZnCN₂ and Pd(PPh₃)₄.

BIOLOGICAL ASSAYS

The ability of compounds of the present invention to inhibit the binding of glucagon and the synthesis or the activity of cytokines can be determined by the following *in vitro* assays.

5

125I-Glucagon Binding Screen with CHO/hGLUR Cells

The reagents are prepared as follows:

1M o-Phenanthroline (Aldrich #32,005-6, MW 198.23)(prepare
10 fresh): 198.2mg/ml ethanol

0.5M DTT (Sigma #D-9779, MW 154.2)(prepare fresh).

Protease Inhibitor Mix(1000X): 5mg leupeptin + 10mg benzamidine +
15 40mg bacitracin + 5mg soybean trypsin inhibitor per ml DMSO. Store
 aliquots at -20°C.

250μM Human Glucagon (Peninsula #7165,MW 3480.62):Solubilize
0.5mg vial in 575ul 0.1N acetic acid.Store in aliquots at -20°C. Thus,
20 1μl yields 1μM final concentration in assay for non-specific binding.

Assay Buffer: 20mM Tris, pH 7.8; 1mM DTT; 3mM o-phenanthroline.

Assay Buffer w/ 0.1% BSA (for dilution of label only, therefore 0.01%
25 final in assay): 10μl 10% BSA (heat-inactivated) + 990μl assay buffer

125I-Glucagon (NEN #NEX-207, receptor-grade, .2200Ci/mmol):
Dilute to 50,000cpm/25μl in assay buffer w/ BSA.Thus, ~50pM final
concentration in assay.

30

Harvesting of CHO/hGLUR Cells for Assay:

1. Remove media from confluent flask then rinse once each with PBS (Ca,Mg-free) and Enzyme-free Dissociation Fluid (Specialty Media, Inc.).

- 102 -

2. Add 10ml Enzyme-free Dissoc. Fluid and hold for ~4min. at 37°C.
3. Gently tap cells free, triturate, take aliquot for counting and centrifuge remainder for 5min. at 1000rpm.
- 5 4. Resuspend pellet in assay buffer (no BSA!) at 75000 cells per 100ul.

10 Alternatively, membrane preparations from CHO/hGLUR cells can be used in place of whole cells at the same assay volume. Final protein concentration of membrane preparation is determined on a per batch basis.

15 The determination of inhibition of glucagon binding is carried out by measuring the reduction of 125 I-glucagon binding in the presence of compounds of Formula I. The assay is carried out in a 96-well box. The following reagents are combined:

		<u>Assay Buffer</u>	<u>Compound /Vehicle</u>	<u>250uM Glucagon</u>	<u>125I- Glucagon</u>	<u>CHO/hGLUR Cells</u>
20	Total Binding	120 μ L	--/5 μ L	--	25 μ L	100 μ L
	+compound	120 μ L	5 μ L/--	--	25 μ L	100 μ L
25	NSB	120 μ L	--/5 μ L	1 μ L	25 μ L	100 μ L

NSB:non specific binding

- 30 The box is incubated for 60min. at 22°C on a shaker at 275rpm. The wells are filtered over pre-soaked (0.5% polyethylimine(PEI)) GF/C filtermat using an Innotech Harvester or Tomtec Harvester with four washes of ice-cold 20mM Tris, pH 7.8 buffer. Count filters in Gamma-scintillation counter.

- 35 Lipopolysaccharide mediated production of cytokines

- Human peripheral blood mononuclear cells (PBMC) are isolated from fresh human blood according to the procedure of Chin and Kostura, *J. Immunol.* **151**, 5574-5585 (1993). Whole blood is collected by sterile venipuncture into 60 mL syringes coated with 1.0 mL of sodium- heparin (Upjohn, 1000 U/mL) and diluted 1:1 in Hanks Balanced Salt Solution (Gibco). The erythrocytes are separated from the PBMC's by centrifugation on a Ficoll-Hypaque lymphocyte separation media. The PBMC's are washed three times in Hanks Balanced Salt Solution and then resuspended to a final concentration of 2×10^6 cell/mL in RPMI containing 10% fresh autologous human serum, penicillin streptomycin (10 U/mL) and 0.05% DMSO. Lipopolysaccharide (Salmonella type Re545; Sigma Chemicals) is added to the cells to a final concentration of 100 ng/mL. An aliquot (0.1 mL) of the cells is quickly dispensed into each well of a 96 well plate containing 0.1 mL of the test compound, at the appropriate dilution, and are incubated for 24 hours. at 37°C in 5% CO₂. At the end of the culture period, cell culture supernatants are assayed for IL-1 β , TNF- α , IL-6 and PGE2 production using specific ELISA.
- 20 IL-1 mediated cytokine production
- Human peripheral blood mononuclear cells are isolated from fresh human blood according to the procedure of Chin and Kostura, *J. Immunol.* **151**, 5574-5585 (1993). Whole blood is collected by sterile venipuncture into 60 mL syringes coated with 1.0 mL of sodium- heparin (Upjohn, 1000 U/mL) and diluted 1:1 in Hanks Balanced Salt Solution (Gibco). The erythrocytes are separated from the PBMC's by centrifugation on a Ficoll-Hypaque lymphocyte separation media. The PBMC's are washed three times in Hanks Balanced Salt Solution and then resuspended to a final concentration of 2×10^6 cell/mL in RPMI containing 10% fresh autologous human serum, penicillin streptomycin (10 U/mL) and 0.05% DMSO. Endotoxin free recombinant human IL-1 β is then added to a final concentration of 50 pMolar. An aliquot (0.1 mL) of the cells is quickly dispensed into each well of a 96 well plate containing 0.1 mL of the compound at the

appropriate dilution, and are incubated for 24 hours, at 37°C in 5% CO₂. At the end of the culture period, cell culture supernatants are assayed for TNF-α, IL-6 and PGE₂ synthesis using specific ELISA.

5 Determination of IL-1β, TNF-α, IL-6 and prostanoid production from LPS or IL-1 stimulated PBMC's

IL-1β ELISA

Human IL-1β can be detected in cell-culture supernatants or whole blood with the following specific trapping ELISA. Ninety-six well plastic plates (Immulon 4; Dynatech) are coated for 12 hours at 4°C with 1 mg/mL protein-A affinity chromatography purified mouse anti-human IL-1b monoclonal antibody (purchased as an ascites preparation from LAO Enterprise, Gaithersburg Maryland.) diluted in Dulbecco's phosphate-buffered saline (-MgCl₂, -CaCl₂). The plates are washed with PBS-Tween (Kirkegaard and Perry) then blocked with 1% BSA diluent and blocking solution (Kirkegaard and Perry) for 60 minutes at room temperature followed by washing with PBS Tween. IL-1β standards are prepared from purified recombinant IL-1β produced from *E. coli*. The highest concentration begins at 10 ng/mL followed by 11 two-fold serial dilution's. For detection of IL-1β from cell culture supernatants or blood plasma, 10 - 25 mL of supernatant is added to each test well with 75 - 90 mL of PBS Tween. Samples are incubated at room temperature for 2 hours then washed 6 times with PBS Tween on an automated plate washer (Dennly). Rabbit anti-human IL-1β polyclonal antisera diluted 1:500 in PBS-Tween is added to the plate and incubated for 1 hour at room temperature followed by six washes with PBS-Tween. Detection of bound rabbit anti-IL-1β IgG is accomplished with Fab' fragments of Goat anti-rabbit IgG-horseradish peroxidase conjugate (Accurate Scientific) diluted 1:10,000 in PBS-Tween. Peroxidase activity was determined using TMB peroxidase substrate kit (Kirkegaard and Perry) with quantitation of color intensity on a 96-well plate Molecular Devices spectrophotometer set to deter-

mine absorbance at 450 nM. Samples are evaluated using a standard curve of absorbance versus concentration. Four-parameter logistics analysis generally is used to fit data and obtain concentrations of unknown compounds.

5

TNF- α ELISA

Immilon 4 (Dynatech) 96-well plastic plates are coated with a 0.5 mg/mL solution of mouse anti-human TNF- α monoclonal antibody. The secondary antibody is a 1:2500 dilution of a rabbit

- 10 anti-human TNF- α polyclonal serum purchased from Genzyme. All other operations are identical to those described above for IL-1 β . The standards are prepared in PBS-Tween + 10% FBS or HS. Eleven 2 fold dilution's are made beginning at 20 ng/mL TNF- α .

15 IL-6 ELISA

Levels of secreted human IL-6 are also determined by specific trapping ELISA as described previously in Chin and Kostura, *J. Immunol.* **151**, 5574-5585 (1993). (Dynatech) ELISA plates are coated with mouse anti-human IL-6 monoclonal antibody diluted to 0.5

- 20 mg/ml in PBS. The secondary antibody, a rabbit anti-human IL-6 polyclonal antiserum, is diluted 1:5000 with PBS-Tween. All other operations are identical to those described above for IL-1 β . The standards are prepared in PBS-Tween + 10% FBS or HS. Eleven 2 fold dilution's are made beginning at 50 ng/mL IL-6.

25

PGE₂ production

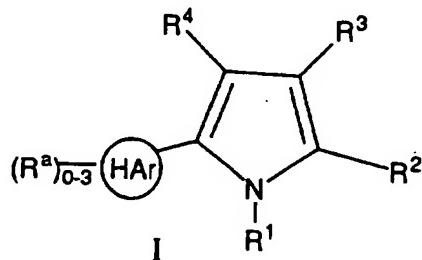
Prostaglandin E2 is detected in cell culture supernatants from LPS or IL-1 stimulated PBMC's using a commercially available enzyme immunoassay . The assay purchased from the Cayman

- 30 Chemical (Catalogue number 514010) and is run exactly according to the manufacturers instructions.

Interleukin8 (IL-8)

- The present compounds can also be assayed for IL-8 inhibitory activity as discussed below. Primary human umbilical cord endothelial cells (HUVEC) (Cell Systems, Kirland, Wa) are maintained in culture medium supplemented with 15% fetal bovine serum and 1%
- 5 CS-HBGF consisting of α FGF and heparin. The cells are then diluted 20-fold before being plated (250 μ l) into gelatin coated 96-well plates. Prior to use, culture medium is replaced with fresh medium (200 μ l). Buffer or test compound (25 μ l, at appropriate concentrations) is then added to each well in quadruplicate wells and the plates incubated for
- 10 6h in a humidified incubator at 37°C in an atmosphere of 5% CO₂. At the end of the incubation period, supernatant is removed and assayed for IL-8 concentration using an IL-8 ELISA kit obtained from R&D Systems (Minneapolis, MN). All data is presented as mean value (ng/ml) of multiple samples based on the standard curve. IC₅₀ values
- 15 where appropriate are generated by non-linear regression analysis.

The following exemplary compounds were found to inhibit cytokine production at an IC₅₀ of less than about 100 μ M and/or inhibit the binding of glucagon to its receptor at an IC₅₀ of less than 2 μ M.



20

Table of Compounds of Formula I with Gluc IC₅₀ < 2.0 μ M and/or Streak IC₅₀ < 4 μ M

R1	(Ra)0-3-Har	R4	R3	R2
H	4-Pyr	4-F-Ph	H	Ph
H	4-Pyr	4-F-Ph	H	4-(SMe)-Ph
H	4-Pyr	4-F-Ph	H	4-(OPh)-Ph
H	4-Pyr	4-F-Ph	H	4-(OEt)-Ph
H	4-Pyr	4-F-Ph	H	4-(CF ₃)-Ph

H	4-Pyr	4-F-Ph	H	4-Br-Ph
H	4-Pyr	4-F-Ph	H	4-(tBu)-Ph
H	4-Pyr	4-F-Ph	H	4-Et-Ph
H	4-Pyr	4-F-Ph	H	4-(SPh)-Ph
H	4-Pyr	4-F-Ph	H	2-Me-Ph
H	4-Pyr	4-F-Ph	H	4-(OMe)-Ph
H	4-Pyr	4-F-Ph	H	4-Me-Ph
H	4-Pyr	4-F-Ph	H	4-Cl-Ph
H	4-Pyr	4-F-Ph	H	4-(OBu)-Ph
H	4-Pyr	4-F-Ph	H	4-(SOMe)-Ph
H	4-Pyr	4-F-Ph	H	4-(OBn)-Ph
H	4-Pyr	4-F-Ph	H	4-F-Ph
H	4-Pyr	4-F-Ph	H	3,4-Cl-Ph
H	4-Pyr	4-F-Ph	H	3-CF ₃ -Ph
H	4-Pyr	4-F-Ph	H	3,4-F-Ph
H	4-Pyr	4-F-Ph	H	3,4-(OCH ₂ O)-Ph
H	4-Pyr	4-F-Ph	H	3-Cl-4-F-Ph
H	4-Pyr	4-F-Ph	H	3-Me-4-Cl-Ph
H	4-Pyr	4-F-Ph	H	4-OCF ₃ -Ph
H	4-Pyr	4-Cl-Ph	H	4-Cl-Ph
H	4-Pyr	4-CF ₃ -Ph	H	4-Cl-Ph
H	4-Pyr	3-Cl-Ph	H	4-Cl-Ph
H	3-Pyr	4-F-Ph	H	4-Cl-Ph
H	4-Pyr	4-OMe-Ph	H	4-Cl-Ph
H	4-Pyr	4-F-Ph	H	4-NO ₂ -Ph
H	4-Pyr	4-F-Ph	H	3-NO ₂ -Ph
H	4-Pyr	4-F-Ph	H	4-(COOEt)-Ph
H	4-Pyr	4-F-Ph	H	4-CN-Ph
H	4-Pyr	4-F-Ph	H	3-CN-Ph
H	4-Pyr	4-F-Ph	H	2-NO ₂ -Ph
H	4-Pyr	4-F-Ph	H	4-(COOH)-Ph
H	4-Pyr	4-F-Ph	H	4-(CH ₂ NH ₂)-Ph
H	4-Pyr	4-F-Ph	H	4-NH ₂ -Ph
H	4-Pyr	4-F-Ph	H	3-NH ₂ -Ph
H	4-Pyr	4-F-Ph	H	2-NH ₂ -Ph
H	2-Pyr	4-F-Ph	H	4-Cl-Ph
H	4-pyr	4-Br-Ph	H	4-Cl-Ph
H	4-Pyr	4-Ph-Ph	H	4-Cl-Ph

H	4-Pyr	4-(4-CF ₃ -Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	3-Br-Ph	H	4-Cl-Ph
H	4-Pyr	4-(4-OMe-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	3-Ph-Ph	H	4-Cl-Ph
H	4-Pyr	3-(4-OMe-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(1-Naphthyl)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(thiophen-2-yl)-Ph	H	4-Cl-Ph
H	4-Pyr	4-tBu-Ph	H	4-Cl-Ph
H	4-Pyr	4-(4-Me-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(4-F-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(3-NO ₂ -Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	3-(3-NO ₂ -Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(thiophen-3-yl)-phenyl	H	4-Cl-Ph
H	4-Pyr	3-(thiophen-2-yl)-phenyl	H	4-Cl-Ph
H	4-Pyr	3-(thiophen-3-yl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(3-(i-Bu)-6-(SO ₂ NH ₂ tBu)-phenyl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(4-(n-Bu)-phenyl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(3-(iBu)-6-(SO ₂ NH ₂)-phenyl)-phenyl	H	4-Cl-Ph
H	4-pyr	3-(4-(n-Bu)-phenyl)-phenyl	H	4-Cl-Ph

H	4-Pyr	4-(5-(n-Bu)-thiophenyl)-phenyl	H	4-Cl-phenyl
H	4-Pyr	2-F-4-Br-phenyl	H	4-Cl-Ph
H	4-Pyr	2-(F)-4-(5-(n-Bu)-thiophen-2-yl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-F-Phenyl	Br	4-Cl-Ph
H	4-Pyr	4-F-phenyl	Cl	4-Cl-phenyl
H	4-pyr	3,5-(Br)-phenyl	H	4-Cl-Ph
H	4-pyr	3,5-(thiophen-2-yl)-phenyl	H	4-Cl-phenyl
H	4-Pyr	CO2Et	H	4-Cl-Ph
H	4-Pyr	3,4-(4-OMe-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	3,5-(4-Me-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(OCH2CO2Me)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(OMe)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(iPr)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(OBn)-Ph	H	4-Cl-Ph
H	4-Pyr	5-(Ph)-thiazol-2-yl	H	4-Cl-Ph
H	4-Pyr	4-(Br)-thiophen-2-yl	H	4-Cl-Ph
H	4-Pyr	2-(OPr)-Ph	H	4-Cl-Ph
H	4-Pyr	3-thiophenyl	H	4-Cl-Ph
H	4-Pyr	CO-(4-(N-phenyl)-piperizinyl)	H	4-Cl-Ph
H	4-Pyr	CONH-2-biphenyl	H	4-Cl-Ph
H	4-Pyr	3,5-(3-nitrophenyl)-phenyl	H	4-Cl-Ph

- 110 -

H	4-Pyr	4-(benzofuran-2-yl)-phenyl	H	4-Cl-Ph
H	4-Pyr	3-Br-5-(thiophen-2-yl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(5-(Cl)-thiophen-2-yl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(3,5-(CF ₃)-phenyl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(2-(OMe)-phenyl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(4-Cl-phenyl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(CO ₂ Me)-phenyl	H	4-Cl-Ph
H	4-Pyr	2-F-4-(thiophen-2-yl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(3-(NH ₂)-phenyl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(3-(OMe)-phenyl)-phenyl	H	4-Cl-Ph
H	4-Pyr	2-Br-Ph	H	4-Cl-Ph
H	4-Pyr	2,6-F-Ph	H	4-Cl-Ph
H	4-Pyr	CONH-adamantyl	H	4-Cl-Ph
H	4-quinolinyl	4-F-Ph	H	4-Cl-Ph
H	4-Pyr	CO ₂ Bn	H	4-Cl-Ph
H	4-Pyr	3-OBn-Ph	H	4-Cl-Ph
H	4-Pyr	4-(t-CHCH-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	9-phenanthrenyl	H	4-Cl-Ph

- 111 -

H	4-Pyr	3-(OPh)-Ph	H	4-Cl-Ph
H	4-Pyr	2-(OMe)-Ph	H	4-Cl-Ph
H	4-Pyr	4-F-Ph	H	2,4-Cl-Ph
H	4-Pyr	4-F-Ph	H	t-Bu
H	4-Pyr	4-F-Ph	H	Me
H	4-Pyr	4-F-Ph	H	4-(N-CBz)-piperidinyl
H	4-pyr	4-CN-phenyl	H	4-Cl-phenyl
H	4-Pyr	2,4-F-Phenyl	H	4-Cl-Ph
H	4-Pyr	2,4,6-F-phenyl	H	4-Cl-phenyl
H	4-Pyr	2-(3-OMe-phenyl)-phenyl	H	4-Cl-phenyl
H	4-Pyr	2-(3-NO ₂ -phenyl)-phenyl	H	4-Cl-phenyl
H	4-Pyr	2-(thiophen-2-yl)-phenyl	H	4-Cl-phenyl
H	4-pyr	2-indolyl	H	4-Cl-Ph
H	4-Pyr	2-(OEt)-phenyl	H	4-Cl-phenyl
H	4-pyr	2-(OMe)-5-(Br)-phenyl	H	4-Cl-phenyl
H	4-pyr	5-(2-(CO ₂ Me)-thiophen-3-yl)-furan-2-yl	H	4-Cl-phenyl
H	4-pyr	2,5-(OMe)-phenyl	H	4-Cl-phenyl
H	4-pyr	4-F-phenyl	H	3-Cl-phenyl
H	4-pyr	4-F-phenyl	H	4-F-phenyl
H	4-Pyr	4-(2-thiophenyl)-phenyl	H	4-F-Ph
H	4-Pyr	4-F-phenyl	H	2-F-phenyl
H	4-Pyr	2-F-4-(2-(5-Cl-thiophen-2-yl)-phenyl	H	4-Cl-phenyl

H	4-Pyr	4-(CONHtBu)-phenyl	H	4-Cl-phenyl
H	4-pyr	4-F-phenyl	H	2-(OMe)-4-(Cl)-phenyl
H	4-(2-F)-pyr	4-F-phenyl	H	4-Cl-phenyl
H	4-pyr	4-(N-methyltetrazol-yl)-phenyl	H	4-Cl-phenyl
H	4-pyr	2-(Cl)-4-(Br)-phenyl	H	4-Cl-phenyl
H	4-pyr	4-(CO2Et)-phenyl	H	4-Cl-phenyl
H	4-Pyr	4-F-phenyl	H	4-N-(acetyl)-piperidinyl
H	4-Pyr	4-F-phenyl	H	4-N-(Me)-piperidinyl
H	4-pyr	4-F-phenyl	H	4-N-(methoxycarbonyl)-piperidinyl
H	4-Pyr	4-F-phenyl	H	4-N-(isopropoxycarbonyl)-piperidinyl
H	4-Pyr	4-F-phenyl	H	4-piperidinyl
H	3-F-4-pyr	4-F-phenyl	H	4-Cl-phenyl
H	3-(Me)-4-pyridyl	4-F-phenyl	H	4-Cl-phenyl
H	4-pyr	2-(ethoxy)-5-(Br)-phenyl	H	4-Cl-phenyl
H	4-pyr	2,5-(F)-phenyl	H	4-Cl-phenyl
H	4-Pyr	2-(3-(Cl)-propoxy)-phenyl	H	4-Cl-Phenyl
H	4-Pyr	2-(propoxy)-5-(Br)-phenyl	H	4-Cl-phenyl
H	4-Pyr	2-(F)-5-(Br)-Phenyl	H	4-Cl-Phenyl
H	4-pyr	4-(CONBn2)-Ph	H	4-Cl-Phenyl

H	4-Pyr	4-(3-Pyr)-phenyl	H	4-Cl-phenyl
H	4-pyr	4-(CO-(N-Boc-piperazin))-phenyl	H	4-Cl-phenyl
H	4-pyr	4-(CONPn2)-phenyl	H	4-Cl-phenyl
H	4-pyr	4-(CO-morpholinyl)-phenyl	H	4-Cl-phenyl
H	4-Pyr	4-(CO-L-proline-OtBu)-phenyl	H	4-Cl-phenyl
H	4-Pyr	4-(CO-spiroindene)-phenyl	H	4-Cl-phenyl
H	4-pyr	4-(5-(Me)-1,3,4-oxadiazol-2-yl)-phenyl	H	4-Cl-phenyl
H	4-Pyr	4-(5-(Bu)-1,3,4-oxadiazol-2-yl)-phenyl	H	4-Cl-phenyl
H	4-pyr	CO2-(2-phenyl-phenyl)	H	4-Cl-phenyl
H	4-(2-methyl)-pyridyl	4-F-phenyl	H	4-Cl-phenyl
H	4-pyr	t-CHCHphenyl	H	4-Cl-phenyl
H	4-pyr	2-(t-CHCH-phenyl)-phenyl	H	4-Cl-phenyl
H	4-pyr	2-(OBn)-phenyl	H	4-Cl-phenyl
H	4-Pyr	2-(O-hexyl)-phenyl	H	4-Cl-phenyl

H	4-pyr	2-(O-nonyl)-phenyl	H	4-Cl-phenyl
H	4-pyr	2-(O-iPr)-phenyl	H	4-Cl-phenyl
H	4-pyr	2-(O-iBu)-phenyl	H	4-Cl-phenyl
H	4-pyr	2-(O-butyl)-phenyl	H	4-Cl-phenyl
H	4-pyr	2-(O-allyl)-phenyl	H	4-Cl-phenyl
H	4-pyr	2-(OCH2-2,6-(Cl)-phenyl)-phenyl	H	4-Cl-phenyl
H	4-pyr	4-(2-pyr)-phenyl	H	4-Cl-phenyl
2-OH-phenyl	4-pyr	2-F-4-Br-phenyl	H	4-Cl-phenyl
H	4-pyr	4-(2-SO2NHtBu-phenyl)-2-F-phenyl	H	4-Cl-phenyl
H	4-pyr	4-NO2-phenyl	H	4-Cl-phenyl
H	4-pyr	4-F-phenyl	H	c-hexyl
H	4-pyr	CO2Et	H	N-(CBz)-piperidin-4-yl
H	4-pyr	4-NH2-phenyl	H	4-Cl-phenyl
H	4-pyr	4-(NHCO2-butyI)-phenyl	H	4-Cl-phenyl
H	4-pyr	4-F-phenyl	Me	4-Cl-phenyl
H	4-Pyr	4-F-Ph	CN	4-Cl-Ph
H	4-pyr	4-(NHSO2-butyI)-phenyl	H	4-Cl-phenyl
H	4-pyr	2-(OCO-propyl)-phenyl	H	4-Cl-phenyl
H	4-pyr	2-(O-(CH2)3-SMe)-phenyl	H	4-Cl-phenyl

H	4-Pyr	4-(NHCO2Bn)-phenyl	H	4-Cl-phenyl
H	4-pyr	4-(NHCO2phenyl)-phenyl	H	4-Cl-phenyl
H	4-Pyr	4-F-Ph	H	N-(COOCH2Ph-4-Cl)-piperidin-4-yl
H	4-pyr	4-F-Ph	H	N-(COOCH2Ph-4-Br)-piperidin-4-yl
H	4-pyr	4-F-Ph	H	N-(COOCH2Ph-4-Ph)-piperidin-4-yl
H	4-Pyr	4-F-Ph	H	N-(COOCH2Ph-4-NO ₂)-piperidin-4-yl
H	4-Pyr	4-F-Ph	H	N-(COOCH2Ph-3-Cl)-piperidin-4-yl
H	4-Pyr	4-F-Ph	H	N-(COOCH2Ph-2,4,5-OMe)-piperidin-4-yl
H	4-Pyr	4-F-Ph	H	N-(COOCH2Ph-2-Cl)-piperidin-4-yl
H	4-Pyr	4-F-Ph	H	4-(NHCBz)-cyclohexyl
H	4-Pyr	4-F-Ph	H	N-(COOCH2Ph)-piperidin-3-yl
H	4-Pyr	4-F-Ph	ethyl	4-Cl-Ph
H	4-Pyr	4-F-Ph	Ph	4-Cl-Ph
H	4-Pyr	4-F-Ph	H	4-(NH ₂)-cyclohexyl
H	4-Pyr	4-F-Ph	H	piperidin-3-yl
H	4-Pyr	2-(hydroxy)-Ph	H	4-Cl-Ph
H	4-Pyr	2-(4-(Cl)-SPh)-Ph	H	4-Cl-Ph

H	4-Pyr	2-(OPh)-Ph	H	4-Cl-Ph
H	4-Pyr	2-(O(CH ₂) ₃ OMe)-Ph	H	4-Cl-Ph
H	4-Pyr	2-(OCONMe ₂)-Ph	H	4-Cl-Ph
H	4-Pyr	2-(S-tBu)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(OPr)-Ph	H	4-Cl-Ph
H	4-Pyr	2-(F)-4-(2-pyridyl)-Ph	H	4-Cl-Ph
H	4-Pyr	2-(OPr)-4-(Br)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(5-((CH ₂) ₄ -OH)-thiophen-2-yl)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(5-((CH ₂) ₄ -azido)-thiophen-2-yl)-Ph	H	4-Cl-Ph
H	4-Pyr	N-(2,6-(Me)-Ph)-piperazin-4-yl-CO-	H	4-Cl-Ph
H	4-Pyr	4-(3-OMe-Ph)-2-(OPr)-Ph	H	4-Cl-Ph
H	4-Pyr	3-(OPr)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(3-NH ₂ -Ph)-2-(OPr)-Ph	H	4-Cl-Ph
H	4-Pyr	benzyl	H	4-Cl-Ph
H	4-Pyr	2-(furan-2-yl)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(furan-2-yl)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(2-(OH)-5-((Br)-Ph))-2-(OPr)-Ph	H	4-Cl-Ph

H	4-Pyr	4-(5-(Bu)-thiophen-2-yl)-2-(OPr)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(3-(OBu)-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(5-((CH ₂) ₄ -amino)-thiophen-2-yl)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(Bu)-thiophen-2-yl)-Ph	H	4-Cl-Ph
H	4-Pyr	1-naphthyl	H	4-Cl-Ph
H	4-pyr	quinolin-8-yl	H	4-Cl-Ph
H	4-Pyr	4-(2-(OMe)-5-(Br)-Ph)-2-(OPr)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(cyclohexyl)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(Bu)-Ph	H	4-Cl-Ph
H	2-(amino)-pyridin-4-yl	4-F-Ph	H	4-Cl-Ph
H	pyrimidin-4-yl	4-F-Ph	H	4-Cl-Ph
H	4-Pyr	4-(5-(NO ₂)-thiophen-2-yl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(3-(Me)-thiophen-2-yl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(2,5-(OMe)-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(2,4,6-(Me)-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(5-(ethyl)-thiophen-2-yl)-Ph	H	4-Cl-Ph

H	4-Pyr	4-(5-(Me)-thiophen-2-yl)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(5-(propyl)-thiophen-2-yl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(4-(Pr)-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-I-Ph	H	4-Cl-Ph
H	4-Pyr	4-(5-(OMe)-pyridin-2-yl)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(3-(Me)-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(3,4-(methylenedioxy)-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(3-(propoxy)-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(3-(acetyl)-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(3-(NO ₂)-4-(Me)-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(3,4-(OMe)-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(3-(OCH ₂ CH ₂ O Me)-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(4-(CN)-3-(Me)-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(5-(acetyl)-thiophen-2-yl)-phenyl	H	4-Cl-Ph
H	4-Pyr	CH ₂ CH ₂ Ph	H	4-Cl-Ph
H	4-Pyr	CH ₂ CH(Me)Ph	H	4-Cl-Ph

H	4-Pyr	CH(Me)CH2-(3,4-(methylenedioxy)-Ph)	H	4-Cl-Ph
H	4-Pyr	4-(3-(OCH2CH2OEt)-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-((indane-1-one)-5-yl)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(4-(Et)-Ph)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(2-trimethylsilyl ethynyl)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(ethynyl)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(5-(CO2Et)-furan-2-yl)-phenyl	H	4-Cl-Ph
H	4-pyr	4-(2-phenylethynyl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(2-(ethyl)-phenyl)-Ph	H	4-Cl-Ph
H	quinolin-6-yl	4-(F)-phenyl	H	4-Cl-Ph
H	4-pyr	4-(2-(n-butyl)-ethynyl)-phenyl	H	4-Cl-Ph
H	4-pyr	4-(2-(4-methyl-phenyl)-ethynyl)-phenyl	H	4-Cl-Ph
H	4-Pyr	2,4-(propoxy)-phenyl	H	4-Cl-Ph
H	4-Pyr	2-(propoxy)-5-(F)-phenyl	H	4-Cl-Ph

- 120 -

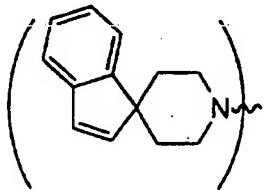
H	4-pyr	3,5-(Br)-2-(propoxy)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(2-(4-(Cl)-phenyl)-ethynyl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(2-(2-pyr)-ethynyl)-phenyl	H	4-Cl-Ph
H	4-Pyr	2-(propoxy)-5-(Cl)-phenyl	H	4-Cl-Ph
H	4-Pyr	2-(propoxy)-3-(Cl)-phenyl	H	4-Cl-Ph
H	4-Pyr	2-(propoxy)-3-(F)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(5-pyrimidinyl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(2-(4-(F)-phenyl)-ethynyl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(2-(4-(ethyl)-phenyl)-ethynyl)-phenyl	H	4-Cl-Ph
H	4-Pyr	4-(2-(4-(butyl)-phenyl)-ethynyl)-phenyl	H	4-Cl-Ph
H	2-(F)-pyridin-5-yl	4-F-Ph	H	4-Cl-Ph
H	4-Pyr	cyclohexyl	H	4-Cl-Ph
H	4-Pyr	4-F-Ph	H	2-Br-Ph
H	4-Pyr	3-(CF ₃)-Ph	Me	N-methyl-piperidin-4-yl
H	4-Pyr	3-(CF ₃)-Ph	Me	piperidin-4-yl

- 121 -

H	2-F-pyridin-5-yl	4-F-Ph	H	4-Cl-Ph
H	2-OH-pyridin-5-yl	4-F-Ph	H	4-Cl-Ph
H	4-Pyr	2-propoxy-4-(2-Ph-ethynyl)-Ph	H	4-Cl-Ph
H	4-Pyr	4-(2-propenyl)-cyclohexen-1-yl	H	4-Cl-Ph
H	4-Pyr	N-(Cbz)-piperidin-4-yl	H	4-Cl-Ph
H	4-Pyr	i-Propyl	H	4-Cl-Ph
H	pyridazin-4-yl	4-F-Ph	H	4-Cl-Ph
H	4-Pyr	4-F-Ph	H	2-CN-Ph
H	4-Pyr	2-CN-Ph	H	4-Cl-Ph
H	4-Pyr	4-F-Ph	n-Bu	4-Cl-Ph

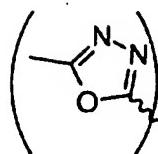
wherein: CO = carbonyl, Ph=phenyl, pyr=pyridyl, Pip=piperidinyl,
 OMe= methoxy, iPr=isopropyl, thioPh-thiophenyl, (A)=SO₂NH₂tBu,
 5 (B)=SO₂NH₂, (C)=SO₂NHCO₂nBu, (D)=tetrazol-5-yl, (E)=5-(n-Bu)-
 thiophen-2-yl, (G)=5-(Cl)-thiophen-2-yl, (J)=N-methyltetrazolyl,
 (M)=N-Boc-piperazin, (Q)=CO-spiroindane-1, (W)=CO-L-proline-
 OtBu, (X)=2-OH-Ph, (Y)=2-SO₂NH₂tBu-Ph, (Z)=piperidin-4-yl,

10 spiroindene-1 is:

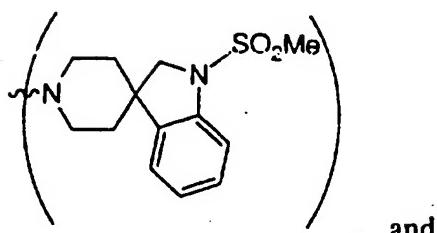


heterocycle-1 is:

- 122 -



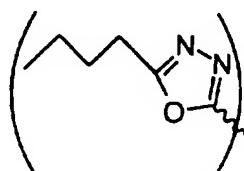
spiroindane-1 is:



, and

5

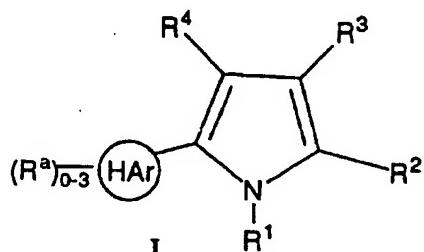
heterocycle-2 is:



- 123 -

WHAT IS CLAIMED IS:

1. A compound represented by formula I:



5

or a pharmaceutically acceptable salt, solvate, hydrate or tautomer thereof, wherein:

(HAr)

represents a heteroaryl group containing from 5 to

- 10 10 atoms, 1-4 of which are heteroatoms, 0-4 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 0-3 Ra groups;

- 15 each Ra independently represents a member selected from the group consisting of: halo, aryl(Rb)0-2, heteroaryl(Rb)0-2, CF₃, OCF₃, CN, NO₂, R²¹, OR²³; SR²³, S(O)R²³, SO₂R²¹, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, NR²⁰SO₂R²¹, NR²⁰C(NR²⁰)NHR²³, COR²⁰, CO₂R²³, CONR²⁰R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, SO₂NR²⁰CO₂R²¹,
20 OCONR²⁰R²³, OCONR²⁰SO₂R²¹, C(NR²⁰)NR²⁰R²³, C(O)OCH₂OC(O)R²⁰, CONR²⁰SO₂R²¹ and SO₂NR²⁰CO₂R²¹;

- when present, each Rb independently represents a member selected from the group consisting of: halo, CF₃, OCF₃, CN, NO₂, OR²³; SR²³, S(O)R²³, SO₂R²¹, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, NR²⁰SO₂R²¹, NR²⁰C(NR²⁰)NHR²³, COR²⁰, CO₂R²³, CONR²⁰R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³,

OCONR²⁰SO₂R²¹, C(NR²⁰)NR²⁰R²³, C(O)OCH₂OC(O)R²⁰,
CONR²⁰SO₂R²¹, and SO₂NR²⁰CO₂R²;

- R¹ is selected from the group consisting of: H, aryl, C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl and heterocyclyl, said alkyl, aryl, alkenyl, alkynyl and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: aryl, heteroaryl, heterocyclyl, halo, OR²³, SR²³, N(R²³)₂, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹,
- NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, COR²⁰, CO₂R²³, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³ and C(O)OCH₂OC(O)R²⁰;
- R² is selected from the group consisting of: C₁-15 alkyl, aryl (with the proviso that aryl is not unsubstituted phenyl), heteroaryl (with the proviso that heteroaryl is not unsubstituted pyridyl), C₇-15 alkenyl, C₂-15 alkynyl, CONR²⁰R²³, SO₂R²¹ (wherein R²¹ is not alkyl or C₁-6 alkenyl), SO₂N(R²⁰)₂, SO₂NR²⁰COR²¹,
- SO₂NR²⁰CON(R²⁰)₂, COR²⁰, CO₂R²⁰ (wherein R²⁰ is not C₁-6 alkyl or hydrogen), CONR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹ and heterocyclyl, said alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: halo, C₁-15 alkyl, OCF₃, CF₃, CN, aryl, NO₂, heteroaryl, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², COR²⁰, CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², and OCONR²⁰R²³;
- R³ is selected from the group consisting of: H, aryl, C₁-15 alkyl, C₂-15 alkenyl, C₂-15 alkynyl, halo, NO₂, CN, CONR²⁰R²³, SO₂R²¹, SO₂N(R²⁰)₂, SO₂NR²⁰COR²¹, SO₂NR²⁰CON(R²⁰)₂, COR²⁰, CO₂R²⁰, CONR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹ and

- 125 -

- heterocyclyl, said alkyl, alkenyl, alkynyl, aryl, and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: halo, C₁₋₁₅ alkyl, CF₃, OCF₃, CN, aryl, NO₂, heteroaryl, OR²³, SR²³, N(R²³)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂,
- 5 SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², COR²⁰, CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², OR²⁰ and OCONR²⁰R²³;
- 10 R⁴ is selected from the group consisting of COR²⁰, COOR²⁰, CONR²⁰R²³, aryl, heterocyclyl, C₁₋₁₅ alkyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl, said alkyl, alkenyl and alkynyl group optionally interrupted by 1-2 oxo or heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and said C₁₋₁₅ alkyl, aryl, heterocyclyl, C₃₋₁₅ alkenyl, C₃₋₁₅
- 15 alkynyl being optionally substituted with from 1-3 of R²¹, halo, aryl(R^a)₀₋₃, heteroaryl(R^a)₀₋₃, heterocyclyl, CN, CF₃, NO₂, OR²³, SR²³, NR²⁰R²³, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, OR²⁰CO₂R²³, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, CO₂R²³, COR²⁰,
- 20 CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³,
- $$\begin{array}{c} \text{---C}\equiv\text{C---} \text{C}_6\text{H}_4 \text{---} (\text{R}^{\text{a}})^{0-3} \\ , \\ \text{---C}\equiv\text{C---} \text{Heteroaryl}(\text{R}^{\text{a}})^{0-3} \end{array}$$

$$\begin{array}{c} \text{---HC=HC---} \text{C}_6\text{H}_4 \text{---} (\text{R}^{\text{a}})^{0-3} \\ , \\ \text{---HC=HC---} \text{Heteroaryl}(\text{R}^{\text{a}})^{0-3} \end{array}$$
and

$$\text{C}(\text{O})\text{OCH}_2\text{OC}(\text{O})\text{R}^{20};$$
- 25 R²⁰ represents a member selected from the group consisting of: H, C₁₋₁₅ alkyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl and alkynyl being optionally substituted with 1-3 groups selected from halo, aryl and heteroaryl;
- 30 R²¹ represents a member selected from the group consisting of: C₁₋₁₅ alkyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl, aryl,

- heterocyclyl and heteroaryl; said alkyl, alkenyl or alkynyl being optionally interrupted by 1-2 heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and said alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl being optionally substituted with from 1-3 of halo,
- 5 heterocyclyl, heteroaryl, aryl(R^a)₀₋₂, heteroaryl(R^a)₀₋₂, CN, OR²⁰, O((CH₂)_nO)_mR²⁰, NR²⁰((CH₂)_nO)_mR²⁰ wherein n represents an integer of from 1 to 4, and m represents an integer of from 1 to 4; SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂,
- 10 NR²²C(NR²²)NHR²², CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², OCONHR²⁰R²³ and OCON(R²⁰)₂;

- R²² is selected from the group consisting of: C₁₋₁₅ alkyl,
- 15 C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or heteroaryl groups;

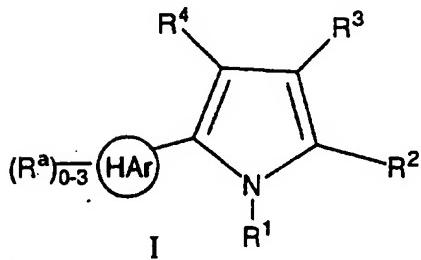
20 R²³ is R²¹ or H;

R²⁴ is selected from aryl, COR²², CO₂R²², CON(R²⁰)₂ and SO₂R²²; and

when two R²⁰ groups are present, R²⁰ and R²¹ are present, or R²⁰ and R²³ are present, said two R²⁰ groups, R²⁰ and R²¹ or said R²⁰ and R²³ may be taken in combination with the atoms to which they are attached and any intervening atoms and represent heterocyclyl containing from 5-10 atoms, at least one atom of which is a heteroatom selected from O, S or N, said heterocyclyl optionally containing 1-3 additional N atoms and 0-1 additional O or S atom.

30

2. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

(HAr)

represents a heteroaryl group containing from 5 to

- 5 10 atoms, 1-4 of which are heteroatoms, 0-4 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 0-3 R^a groups;

each R^a independently represents a member selected from

- 10 the group consisting of: halo, aryl(R^b)0-2, heteroaryl(R^b)0-2, CF₃, OCF₃, CN, NO₂, R²¹, OR²³, SR²³, S(O)R²³, SO₂R²¹, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, NR²⁰SO₂R²¹, NR²⁰C(NR²⁰)NHR²³, COR²⁰, CO₂R²³, CONR²⁰R²³, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, SO₂NR²⁰CO₂R²¹,
15 OCONR²⁰R²³, OCONR²⁰SO₂R²¹, C(NR²⁰)NR²⁰R²³, C(O)OCH₂OC(O)R²⁰, CONR²⁰SO₂R²¹, and SO₂NR²⁰CO₂R²;

R^b is R^a minus aryl, heteroaryl and R²¹;

- 20 R¹ is selected from the group consisting of: H, aryl, C₁₋₁₅ alkyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl and heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: aryl, heteroaryl, heterocyclyl, halo, OR²³, SR²³, N(R²³)₂, S(O)R²¹, SO₂R²¹,
25 SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, COR²⁰, CO₂R²³, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹,

$\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{21}$, $\text{OCONR}^{20}\text{R}^{23}$, $\text{OCONR}^{20}\text{SO}_2\text{R}^{21}$, $\text{OCONR}^{20}\text{R}^{23}$ and
 $\text{C(O)OCH}_2\text{OC(O)R}^{20}$;

- R^2 is selected from the group consisting of: aryl (wherein
- 5 aryl is not unsubstituted phenyl), heteroaryl (wherein heteroaryl is not unsubstituted pyridyl), C₇-15 alkenyl, C₂-15 alkynyl, $\text{CONR}^{20}\text{R}^{23}$, SO_2R^{21} (wherein R²¹ is not alkyl or C₁-6 alkenyl), $\text{SO}_2\text{N}(\text{R}^{20})_2$, $\text{SO}_2\text{NR}^{20}\text{COR}^{21}$, $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, COR^{20} , CO_2R^{20} (wherein R²⁰ is not C₁-6 alkyl or hydrogen), $\text{CONR}^{20}\text{SO}_2\text{R}^{21}$,
 - 10 $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{21}$ and heterocyclyl, said alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: halo, C₁-15 alkyl, OCF_3 , CF_3 , CN, aryl, NO_2 , heteroaryl, OR^{20} , SR^{20} , $\text{N}(\text{R}^{20})_2$, S(O)R^{22} , SO_2R^{22} , $\text{SO}_2\text{N}(\text{R}^{20})_2$, $\text{SO}_2\text{NR}^{20}\text{COR}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$,
 - 15 $\text{NR}^{20}\text{COR}^{22}$, $\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{NR}^{22}\text{C}(\text{NR}^{22})\text{NHR}^{22}$, COR^{20} , CO_2R^{20} , $\text{CON}(\text{R}^{20})_2$, $\text{CONR}^{20}\text{SO}_2\text{R}^{22}$, $\text{NR}^{20}\text{SO}_2\text{R}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{OCONR}^{20}\text{SO}_2\text{R}^{22}$, and $\text{OCONR}^{20}\text{R}^{23}$;

- R^3 is selected from the group consisting of: H, C₁-15 alkyl,
- 20 aryl, C₂-15 alkenyl, C₂-15 alkynyl, halo, NO_2 , CN, $\text{CONR}^{20}\text{R}^{23}$, SO_2R^{21} , $\text{SO}_2\text{N}(\text{R}^{20})_2$, $\text{SO}_2\text{NR}^{20}\text{COR}^{21}$, $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, COR^{20} , CO_2R^{20} , $\text{CONR}^{20}\text{SO}_2\text{R}^{21}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{21}$ and heterocyclyl, said alkyl, alkenyl, alkynyl, aryl, and heterocyclyl being optionally substituted with from one to three members selected from the
 - 25 group consisting of: halo, C₁-15 alkyl, CF_3 , OCF_3 , CN, aryl, NO_2 , heteroaryl, OR^{23} , SR^{23} , $\text{N}(\text{R}^{23})_2$, S(O)R^{22} , SO_2R^{22} , $\text{SO}_2\text{N}(\text{R}^{20})_2$, $\text{SO}_2\text{NR}^{20}\text{COR}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{NR}^{20}\text{COR}^{22}$, $\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$, $\text{NR}^{22}\text{C}(\text{NR}^{22})\text{NHR}^{22}$, COR^{20} , CO_2R^{20} , $\text{CON}(\text{R}^{20})_2$, $\text{CONR}^{20}\text{SO}_2\text{R}^{22}$, $\text{NR}^{20}\text{SO}_2\text{R}^{22}$, $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$, $\text{OCONR}^{20}\text{SO}_2\text{R}^{22}$,
 - 30 OR^{20} and $\text{OCONR}^{20}\text{R}^{23}$;

R^4 is selected from the group consisting of COR^{20} , COOR^{20} , $\text{CONR}^{20}\text{R}^{23}$, aryl, heterocyclyl, C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl, said alkyl, alkenyl and alkynyl group optionally

- interrupted by 1-2 oxo or heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and said C₁-15 alkyl, aryl, heterocyclyl, C₃-15 alkenyl, C₃-15 alkynyl being optionally substituted with from 1-3 of R²¹, halo, aryl(R^a)₀-3, heteroaryl(R^a)₀-3, heterocyclyl, CN, CF₃, NO₂, OR²³,
- 5 SR²³, NR²⁰R²³, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, OR²⁰CO₂R²³, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, CO₂R²³, COR²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³ and
- 10 C(O)OCH₂OC(O)R²⁰;

R²⁰ represents a member selected from the group consisting of: H, C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl and alkynyl being optionally substituted with 1-3 groups selected from halo, aryl and heteroaryl;

- R²¹ represents a member selected from the group consisting of: C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl, aryl, heterocyclyl and heteroaryl; said alkyl, alkenyl or alkynyl being optionally interrupted by 1-2 heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and said alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl being optionally substituted with from 1-3 of halo, heterocyclyl, heteroaryl, aryl(R^a)₀-2, heteroaryl(R^a)₀-2, CN, OR²⁰, O((CH₂)_nO)_mR²⁰, NR²⁰((CH₂)_nO)_mR²⁰ wherein n represents an integer
- 20 of from 1 to 4, and m represents an integer of from 1 to 4; SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², OCONHR²⁰R²³
- 25 and OCON(R²⁰)₂;

R²² is selected from the group consisting of: C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl, heterocyclyl, aryl and heteroaryl, said

alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or heteroaryl groups;

R²³ is R²¹ or H;

5

R²⁴ is selected from aryl, COR²², CO₂R²², CON(R²⁰)₂ and SO₂R²²; and

- in any substituent wherein two R²⁰ groups are present,
wherein R²⁰ and R²¹ are present, or wherein R²⁰ and R²³ are present,
10 said two R²⁰ groups, R²⁰ and R²¹ or said R²⁰ and R²³ may be taken in
combination with the atoms to which they are attached and any
intervening atoms and represent heterocyclyl containing from 5-10
atoms, at least one atom of which is a heteroatom selected from O, S or
N, said heterocyclyl optionally containing 1-3 additional N atoms and 0-1
15 additional O or S atom.

3. A compound in accordance with claim 1 wherein:

- R¹ represents H, alkyl, substituted alkyl, aryl and substituted aryl, said
substituted groups being substituted with from 1 to 3 groups selected
20 from R^a.

4. A compound in accordance with claim 1 wherein:

- R² represents aryl(wherein aryl is not unsubstituted phenyl), heteroaryl
(wherein heteroaryl is not unsubstituted pyridyl), C₁₋₁₅ alkyl, C₇₋₁₅
25 alkenyl, C₂₋₁₅ alkynyl, and heterocyclyl, said alkyl, alkenyl, alkynyl,
aryl, heteroaryl and heterocyclyl groups being unsubstituted or
substituted with 1 to 3 groups of R^a.

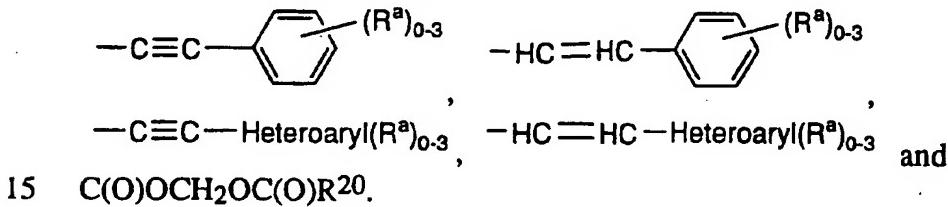
5. A compound in accordance with claim 1 wherein:

- R³ represents H, C₁₋₁₅ alkyl, halo, NO₂, CN, CONR²⁰R²³, SO₂R²¹
and CO₂R²⁰, said alkyl group being unsubstituted or substituted with 1
to 3 groups of R^a.

6. A compound in accordance with claim 1 wherein:

R^4 is aryl, C₁₋₁₅ alkyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl, heterocyclyl, CO₂R²⁰ or CONR²⁰R²³,

- said alkyl, alkenyl and alkynyl group optionally interrupted by 1-2 oxo or heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and
- 5 said C₁₋₁₅ alkyl, aryl, heterocyclyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl being optionally substituted with from 1-3 of R²¹, halo, aryl(R^a)₀₋₃, heteroaryl(R^a)₀₋₃, heterocyclyl, CN, CF₃, NO₂, OR²³, SR²³, NR²⁰R²³, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, OR²⁰CO₂R²³, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³,
- 10 N(R²⁰)C(NR²⁰)NHR²³, CO₂R²³, COR²⁰, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³,



- 15 C(O)OCH₂OC(O)R²⁰.

7. A compound in accordance with claim 1 wherein:
- R^4 is aryl, alkyl, alkenyl, alkynyl, heterocyclyl, CO₂R²⁰ or CONR²⁰R²³, said aryl, alkyl, alkenyl, alkynyl, and heterocyclyl being unsubstituted or substituted with 1 to 3 groups of R^a.

8. A compound in accordance with claim 1 wherein Har represents a member selected from the group consisting of: pyridinyl, quinolyl, purinyl, imidazolyl, imidazopyridinyl, pyrimidinyl, pyrrolyl and triazolyl.

9. A compound in accordance with claim 8 wherein Har represents 3- or 4- pyridinyl.

- 30 10. A compound in accordance with claim 1 wherein from 1-3 R^a groups attached to the Har substituent, independently selected from the group consisting of: halo, aryl(R^b)₀₋₂.

heteroaryl(R^b)O-2, CF₃, OCF₃, NO₂, R²¹, OR²³; SR²³, S(O)R²³, SO₂R²¹, NR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, NR²⁰SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³ and SO₂NR²⁰CO₂R²¹,

5 and R^b, R²⁰, R²¹ R²², R²³ and R²⁴ are as originally defined.

11. A compound in accordance with claim 1 wherein:

10 R¹ is H, aryl, or C₁-15 alkyl;

15 R² is aryl, (wherein aryl is not unsubstituted phenyl), heteroaryl (wherein heteroaryl is not unsubstituted pyridyl) C₇-15 alkenyl, C₂-15 alkynyl, heterocyclyl;

20 R³ is H, halo, NO₂, CO₂R²⁰, CONHiPr or CN; and

25 R⁴ is aryl, C₁-15 alkyl, C₂-15 alkenyl, C₂-15 alkynyl, CO₂R²⁰, CONR²⁰R²³ or heterocyclyl, said aryl, alkyl and heterocyclyl being unsubstituted or substituted with 1 to 3 groups of R^a.

12. A compound in accordance with claim 1 wherein:

30 R¹ is H or aryl;

R² is aryl (wherein aryl is not unsubstituted phenyl), heteroaryl (wherein heteroaryl is not unsubstituted pyridyl), or heterocyclyl;

R³ is H or halo;

35 R⁴ is aryl, C₁-C₆ alkyl, C₂-15 alkenyl, C₂-15 alkynyl, CO₂R²⁰, heterocyclyl or CONR²⁰R²³, said aryl, alkyl and heterocyclyl being unsubstituted or substituted with 1 to 3 groups of R^a and

HAr is

- 5 a) pyridinyl,
- b) quinolyl,
- c) purinyl,
- d) imidazolyl,
- e) imidazopyridinyl or
- f) pyrimidinyl.

13. A compound in accordance with claim 1 wherein
10 (R^a)₀₋₃-HAr is selected from the group consisting of:

- 15 a) 4-pyridinyl,
- b) 2-methyl-4-pyridinyl,
- c) 3-methyl-4-pyridinyl,
- d) 2-amino-4-pyridinyl,
- e) 2-benzylamino-4-pyridinyl,
- f) 2-acetylamino-4-pyridinyl,
- g) 4-quinolinyl-,
- h) 4-(3-F-quinolinyl),
- i) 2-imidazo-(4,5-b)-pyridinyl,
- 20 j) 7-imidazo-(4,3-b)-pyridinyl,
- k) 2-imidazo-(4,5-b)-pyridinyl,
- l) 4-(2-F-pyridinyl),
- m) 4-(3-F-pyridinyl),
- n) 4-(2-SMe-pyrimidinyl),
- 25 o) 4-(2-NH₂-pyrimidinyl),
- p) 4-(2-MeNH-pyrimidinyl),
- q) 2-(NH₂-pyridinyl),
- r) 2-(MeNH-pyridinyl),
- s) 2-(N-benzylamino)pyridinyl,
- 30 t) 3-pyridinyl,
- u) 2-pyridinyl or
- v) 4-(2,6-di-Phenyl)-pyridinyl;

R¹ is

H or 2-OH-Phenyl;

R² is

5

- 1) Cl-Ph,
- 2) Br-Ph,
- 3) F-Ph,
- 4) (C₁-C₄ alkyl)-Ph,
- 5) CF₃-Ph

10

- 6) (O-(C₁-C₄ alkyl))-Ph,
- 7) (C₃-C₆ cycloalkyl)-Ph,
- 8) phenyl-Ph,
- 9) CN-Ph,
- 10) COOH-Ph,
- 11) NO₂-Ph,

15

- 12) SMe-Ph,
- 13) (O-phenyl)-Ph,
- 14) (S-phenyl)-Ph,
- 15) (OBn)-Ph,
- 16) -(S(O)-phenyl)-Ph,
- 17) OCF₃-Ph,

20

- 18) CO₂Et-Ph,
- 19) -S(O)Me-Ph,
- 20) (CH₂NH₂)-Ph,
- 21) NH₂-Ph,

25

- 22) N-CBz-piperdin-4-yl,
- 23) N-Me-piperdin-4-yl,
- 24) t-butyl-Ph,
- 25) 2-thiophenyl,
- 26) 3,4-(OCH₂O)-Ph,
- 27) 3-(Cl)-4-(F)-Ph,

30

- 28) -S(O)Ph,
- 29) 2,4-(Cl)-Phenyl,
- 30) 3,4-(Cl)-Phenyl,
- 31) 2-(OMe)-4-(Cl)Ph,
- 32) 4-N-(acetyl)-piperidinyl,
- 33) 4-N-(OMe-CO)-piperidinyl,

35

- 135 -

- 34) 4-N-(iPr-CO)-piperidinyl,
 - 35) 4-piperidinyl,
 - 36) 4-pyridinyl,
 - 37) c-hexyl,
 - 38) 4-(OBn)-Phenyl,
 - 39) 4-N(CO₂Me)-piperidinyl or
 - 40) 3-(Me)-4-(F)-Phenyl;

5

R^3 is H, Br or Cl;

10

R^4 is

1. 4-(phenyl)-Ph,
 2. 3-(phenyl)-Ph,
 3. 4-(2-thiophenyl)-Ph,
 4. 4-(t-butyl)-Ph,
 5. 4-(toluyl)-Ph,
 6. 4-(4-fluorophenyl)-Ph,
 7. 4-(3-nitro-phenyl)-Ph,
 8. 3-(3-nitro-phenyl)-Ph,
 9. 4-(quinolinyl)-Ph,
 10. Cl-Ph,
 11. OMe-Ph,
 12. Br-Ph,
 13. CF₃-Ph,
 14. (cyclohexyl)-Ph,
 15. (i-butyl)-Ph,
 16. (4-(2-tetrazol-5-yl)-phenyl)-Ph,
 17. 4-(3-thiophenyl)-Ph,
 18. 2-(naphthyl)-Ph,
 19. F-Ph,
 20. hydroxy-Ph,
 21. 4-NMe₂-Ph,
 22. CO₂Et-Ph,
 23. COOH-Ph,

20

25

30

24. 4(OMe)-Ph,
25. 2-(F)-4-(Br)-Ph,
26. 4-(4-CF₃-phenyl)-Ph,
27. 4-(4-OMe-phenyl)-Ph,
5 28. 3-(4-OMe-phenyl)-Ph,
29. 4-(1-naphthyl)-Ph,
30. phenyl,
31. 4-(4-Me-Ph)-Ph,
10 32. 3-(2-thiophenyl)-Ph,
33. 3-(3-thiophenyl)-Ph,
34. 4-(3-(iBu)-6-(SO₂NH₂)-Ph)-Ph,
35. 4-(3-(iBu)-6-(SO₂NH₂t-Bu)-Ph)-Ph,
36. 4-(4-(nBu)-Ph)-Ph,
15 37. 4-(3-(iBu)-6-(SO₂NHCO₂nBu)-Ph)-Ph,
38. 3-(4-(n-Bu)-Ph)-Ph,
39. 4-(3-(n-Pr)-6-(tetrazol-5-yl)-Ph)-Ph,
40. 4-(5-n-Bu)-thiophenyl-Ph,
41. 2-F-4-(2-(5-n-Bu)-thiophenyl)-Ph,
42. 3,5-(2-thiophenyl)phenyl,
20 43. 3,4-(4-OMe-Ph)-Ph,
44. 3,5-(4-Me-Ph)-Ph,
45. 3,5-(4-SMe-Ph)-Ph,
46. 4-(NHCOMe)-Ph,
47. 4-(OCH₂CO₂Me)-Ph,
25 48. 3,5-(di-Bromo)-Ph,
49. 4-(iPr)-Ph,
50. 4-(OBn)-Ph,
51. 2-(OPr)-Ph,
52. -CONHBn,
30 53. -CON-((4-benzyl)-piperidinyl),
54. -CONHPh,
55. -CO-(4-N-phenyl-piperizin-1-yl),
56. -CONH-((2-(2-indolyl)-phenyl),
57. -CONH-4-biphenyl,

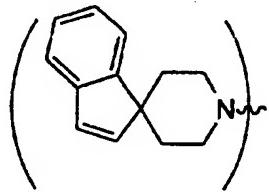
- 5 58. -CONH-2-biphenyl,
 59. 3,5-(3-nitrophenyl)-phenyl,
 60. 4-(2-benzofuranyl)-phenyl,
 61. 3-Br-5-(2-thiophenyl)-phenyl,
 62. 4-(2-(5-Cl)-thiophenyl)-phenyl,
 63. 4-(3,5-(CF₃)-phenyl)-phenyl,
 64. 4-(2-(OMe)-phenyl)-phenyl,
 65. 4-(4-Cl-phenyl)-phenyl,
 66. 4-(CO₂Me)-phenyl,
- 10 67. 2-F-4-(2-thiophenyl)-phenyl,
 68. 4-(3-(NH₂)-phenyl)-phenyl,
 69. 4-(3-(OMe)-phenyl)-phenyl,
 70. 2,6-F-Ph,
 71. -CONH-2-fluorenyl,
 72. -CONH-(4-(n-octyl)-phenyl),
 73. -CONH-adamantyl,
 74. -CONH-c-hexyl,
 75. -CONH-CH(Bn)₂,
 76. -CONHCH(Ph)₂,
 77. -CONHCH₂CH-(Ph)₂,
 78. -CONH-2-tetrahydro-isoquinolinyl,
 79. -CO₂Bn,
 80. 3-(OBn)-Ph,
 81. 4-(CHCH-Ph)-Ph,
 82. 9-phenanthrenyl,
 83. 3-(OPh)-Ph,
 84. 2-(OMe)-Ph,
 85. CO₂Et,
 86. COOH,
 87. 4-CN-Phenyl,
 88. 2,4-F-Phenyl,
 89. 2,4,6,-F-Phenyl,
 90. 2-(3-OMe-Ph)-Ph,
 91. 2-(3-NO₂-Ph)-Ph,
- 15
20
25
30

- 5 92. 2-(thiophen-2-yl)-Ph,
 93. 2-(OEt)-Ph,
 94. 2-(OH)-5-(Br)-Ph,
 95. 2-(OMe)-5-(Br)-Ph,
 96. 2,5-(OMe)-Ph,
 97. 4-(tetrazol-5-yl)-Ph,
 98. 2-F-(4-(Cl)-thiophen-2-yl)-Ph,
 99. 4-(CONHtBu)-Ph,
 100. 4-(N-methyl-tetrazol-5-yl)-Ph,
10 101. 2-(Cl)-4-(Br)-Ph,
 102. 2-(ethoxy)-5-(Br)-Ph,
 103. 2,5-F-Ph,
 104. 2-(3-(Cl)-propoxy)-Ph,
 105. 2-(propoxy)-5-(Br)-Ph,
15 106. 2-(F)-5-(Br)-Ph,
 107. 4-(CON(Bn₂))-Ph,
 108. 4-(3-Pyr)-Ph,
 109. 4-(CO-(N-Boc-piperazin)-Ph,
 110. 4-(CONPn₂)-Ph,
20 111. 4-(CO-morpholinyl)-Ph,
 112. 4-(CO-L-proline-OtBu)-Ph,
 113. 4-(CO-spiroindane-1)-Ph,
 114. 4-(CO-spiroindene-1)-Ph,
 115. 4-(CON(Me)₂)-Ph,
25 116. 4-(heterocycle-1)-Ph,
 117. 4-(heterocycle-2)-Ph,
 118. CO₂-(2-Ph-Ph),
 119. CHCHPh,
 120. 2-(OBn)-Ph,
30 121. 2-(O-hexyl)-Ph,
 122. 2-(O-nonyl)-Ph,
 123. 2-(O-iPr)-Ph,
 124. 2-(O-iBu)-Ph,
 125. 4-(2-pyr)-Ph,

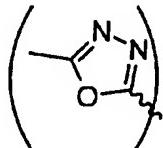
- 139 -

- 126. 4-(2-SO₂NH₂tBu-Ph)-2-F-Ph
- 127. 4-NO₂-Ph,
- 128. 4-NH₂-Ph or
- 129. 4-(NHCO₂-butyl)-Ph

5 wherein:
spiroindene-1 is:

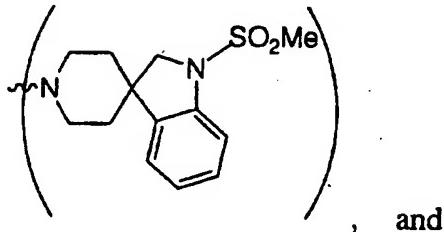


heterocycle-1 is:



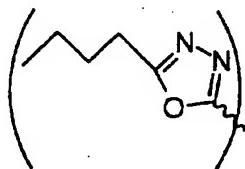
10

spiroindane-1 is:



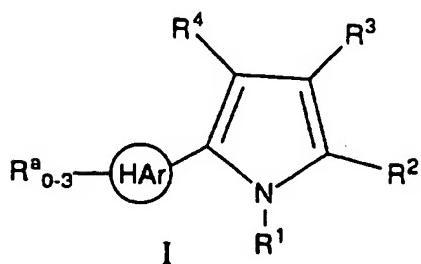
, and

15 heterocycle-2 is:



- 140 -

14. A compound of the formula:



5 or a pharmaceutically acceptable salt thereof, wherein:

(HAr)

represents a heteroaryl group containing from 5 to 10 atoms, 1-3 of which are heteroatoms, 0-3 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being substituted 10 with 1-3 R^a groups;

each R^a independently represents a member selected from the group consisting of: halo; CN, NO₂, R²¹; OR²³; SR²³; S(O)R²¹; SO₂R²¹; NR²⁰R²³; NR²⁰COR²¹; NR²⁰CO₂R²¹; NR²⁰CONR²⁰R²³; 15 NR²⁰SO₂R²¹; NR²⁰C(NR²⁰)NHR²³, CO₂R²³; CONR²⁰R²³; SO₂NR²⁰R²³; SO₂NR²⁰COR²¹; SO₂NR²⁰CONR²⁰R²³; SO₂NR²⁰CO₂R²¹; OCONR²⁰R²³; OCONR²⁰SO₂R²⁰; C(NR²⁰)NR²⁰R²³; 20 C(O)OCH₂OC(O)R²⁰; CONR²⁰SO₂R²¹; and SO₂NR²⁰CO₂R²¹, tetrazol-5-yl;

20 R¹ is selected from the group consisting of: H, aryl, C₁₋₁₅ alkyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl; and heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: aryl, heteroaryl, heterocyclyl, halo, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, CO₂R²³, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹,

OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³ and
C(O)OCH₂OC(O)R²⁰;

- R² is selected from the group consisting of: aryl,
 5 heteroaryl, heterocyclyl, C₁-15 alkyl, C₂-15 alkenyl, C₂-15 alkynyl,
 said alkyl, alkenyl and alkynyl group optionally interrupted by 1-2
 heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and said aryl,
 heteroaryl, heterocyclyl, alkyl, alkenyl, alkynyl being optionally
 substituted with from 1-3 of halo, aryl, heteroaryl, aryl(R^a)₁₋₂, C₁-15
 10 alkyl, heteroaryl(R^a)₁₋₂, CN, CF₃, NO₂, heterocyclyl, OR²³, SR²³,
 NR²⁰R²³, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹,
 SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³,
 N(R²⁰)C(NR²⁰)NHR²³, CO₂R²³, COR²¹, CONR²⁰R²³,
 CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³,
 15 OCONR²⁰SO₂R²¹, OCONR²⁰R²³ and C(O)OCH₂OC(O)R²⁰;

- R³ is selected from the group consisting of: H, C₁-15 alkyl,
 aryl, C₂-15 alkenyl, C₂-15 alkynyl, halo, NO₂, CO₂R²², CN,
 CONR²⁰R²³, SO₂R²¹, SO₂N(R²⁰)₂, SO₂NR²⁰COR²¹,
 20 SO₂NR²⁰CON(R²⁰)₂, COR²¹, CO₂R²⁰, CONR²⁰SO₂R²¹,
 SO₂NR²⁰CO₂R²¹, and heterocyclyl, said alkyl, alkenyl, alkynyl, aryl,
 and heterocyclyl being optionally substituted with from one to three
 members selected from the group consisting of: halo, C₁-15 alkyl, CF₃,
 CN, aryl, NO₂, heteroaryl, OR²⁰, SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²²,
 25 SO₂N(R²⁰)₂, SO₂NR²⁰COR²², SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²²,
 NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², CO₂R²⁰,
 CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²²,
 OCONR²⁰SO₂R²², OR²⁰ and OCONR²⁰R²³;
- 30 R⁴ is selected from the group consisting of COR²¹, CONR²⁰R²³,
 aryl, heteroaryl, heterocyclyl, C₁-15 alkyl, C₃-15 alkenyl, C₃-15 alkynyl,
 said alkyl, alkenyl and alkynyl group optionally interrupted by 1-2
 heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and said aryl,
 heteroaryl, heterocyclyl, C₃-15 alkenyl, C₃-15 alkynyl being optionally

- substituted with from 1-3 of R²¹, halo, CN, CF₃, NO₂, OR²³, SR²³, NR²⁰R²³, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹, SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, CO₂R²³, COR²¹, CONR²⁰R²³,
- 5 CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³ and C(O)OCH₂OC(O)R²⁰; said alkyl being optionally substituted with aryl, heteroaryl, heterocyclyl, being optionally substituted with from 1-3 of R²¹, halo, CN, CF₃, NO₂, OR²³, SR²³, NR²⁰R²³, S(O)R²¹, SO₂R²¹, SO₂NR²⁰R²³, SO₂NR²⁰COR²¹,
- 10 SO₂NR²⁰CONR²⁰R²³, NR²⁰COR²¹, NR²⁰CO₂R²¹, NR²⁰CONR²⁰R²³, N(R²⁰)C(NR²⁰)NHR²³, CO₂R²³, COR²¹, CONR²⁰R²³, CONR²⁰SO₂R²¹, NR²⁰SO₂R²¹, SO₂NR²⁰CO₂R²¹, OCONR²⁰R²³, OCONR²⁰SO₂R²¹, OCONR²⁰R²³ and C(O)OCH₂OC(O)R²⁰;
- 15 R²⁰ represents a member selected from the group consisting of: H, C₁₋₁₅ alkyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl and alkynyl being optionally substituted with 1-3 groups selected from halo, aryl and heteroaryl;
- 20 R²¹ represents a member selected from the group consisting of: C₁₋₁₅ alkyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl, aryl, heterocyclyl and heteroaryl; said alkyl, alkenyl or alkynyl being optionally interrupted by 1-2 heteroatoms selected from O, S, S(O), SO₂ or NR²⁴ and said alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl being optionally substituted with from 1-3 of halo, heterocyclyl, aryl, heteroaryl, aryl(R^a)₁₋₂, heteroaryl(R^a)₁₋₂, CN, OR²⁰, O((CH₂)_nO)_mR²⁰, NR²⁰((CH₂)_nO)_mR²⁰ wherein n represents an integer of from 2 to 4, and m represents an integer of from 1 to 3; SR²⁰, N(R²⁰)₂, S(O)R²², SO₂R²², SO₂N(R²⁰)₂, SO₂NR²⁰COR²²,
- 25 SO₂NR²⁰CON(R²⁰)₂, NR²⁰COR²², NR²⁰CO₂R²², NR²⁰CON(R²⁰)₂, NR²²C(NR²²)NHR²², CO₂R²⁰, CON(R²⁰)₂, CONR²⁰SO₂R²², NR²⁰SO₂R²², SO₂NR²⁰CO₂R²², OCONR²⁰SO₂R²², OCONHR²⁰R²³ and OCON(R²⁰)₂;
- 30

R²² is selected from the group consisting of: C₁₋₁₅ alkyl, C₃₋₁₅ alkenyl, C₃₋₁₅ alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or heteroaryl groups;

5

R²³ is R²¹ or H;

R²⁴ is selected from aryl, COR²², CO₂R²², CON(R²⁰)₂ and SO₂R²²;

10

n is 1-4;

m is 1-4;

15

and in a functional group substituent wherein two R²⁰ groups are present, when R²⁰ and R²¹ are present, or when R²⁰ and R²³ are present, said two R²⁰ groups, R²⁰ and R²¹ or said R²⁰ and R²³ may be taken in combination with the atoms to which they are attached and any intervening atoms and represent heterocyclyl containing from 5-10 atoms, at least one atom of which is a heteroatom selected from O, S or N, said heterocyclyl optionally containing 1-3 additional N atoms and 0-1 additional O or S atom.

20

15. A compound in accordance with claim 14 wherein:

25

R¹ is H, aryl, or C₁₋₁₅ alkyl, wherein H, aryl and C₁₋₁₅ alkyl are defined above;

30

R² is aryl, C₁₋₁₅ alkyl, heteroaryl, or heterocyclyl, wherein aryl, C₁₋₁₅ alkyl, heteroaryl, or heterocyclyl are defined above;

R³ is H, halo, NO₂, or CN; and

R⁴ is aryl, C₁-15 alkyl, heteroaryl, COR²¹, CONR²⁰R²³ or heterocyclyl, wherein aryl, C₁-15 alkyl, heteroaryl, COR²¹, CONR²⁰R²³ or heterocyclyl are defined above.

5 16. A compound in accordance with claim 14

wherein:

R¹ is H, or substituted alkyl;

R² is aryl, C₁-C₆- alkyl, heteroaryl, or

10 heterocyclyl; wherein aryl, C₁-C₆ alkyl, heteroaryl, and heterocyclyl are defined above;

R⁴ is aryl, C₁-C₆ alkyl, heteroaryl, heterocyclyl, or

15 CONR²⁰R²³; wherein aryl, C₁-C₆ alkyl, heteroaryl, R²⁰ and R²³ and heterocyclyl are defined above;

R₃ is H or halo; and

HAr is a) pyridyl,

20 b) quinolyl,

c) purinyl,

d) imidazolyl,

e) imidazopyridinyl, or

f) pyrimidinyl.

25

17. A compound in accordance with claim 14 wherein

HAr is a) 4-pyridyl-,

b) (2-methyl-4-pyridyl)-,

c) (3-methyl-4-pyridyl)-,

30 d) (2-amino-4-pyridyl)-,

e) (2-benzylamino-4-pyridyl)-,

f) (2-acetylamino-4-pyridyl)-,

g) 4-quinolyl-,

h) (4-(2-methoxy)-pyridyl)-,

- 145 -

- i) 4-pyrimidinyl-,
- j) 9-purinyl-, or
- k) 7-(imidazo[4,5-b]pyridinyl)-;

5 R¹ is H;

R² is phenyl substituted with:

- a) Cl,
- b) Br,
- c) F,
- d) C₁-C₄ alkyl,
- e) CF₃,
- f) O-(C₁-C₄ alkyl),
- g) C₃-C₆ cycloalkyl,
- h) phenyl,
- i) CN,
- j) COOH,
- k) NO₂,
- l) alkyl-N(alkyl)₂,
- m) NHCO-alkyl or
- n) CONHalkyl;

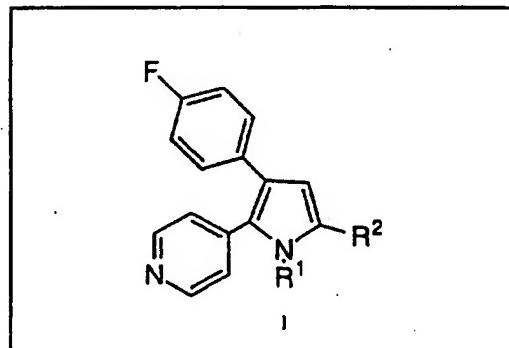
R³ is H

- 25 R⁴ is
- a) phenyl optionally substituted with:
 - 1. 4-phenyl,
 - 2. 3-phenyl,
 - 3. 4-(2-thiophenyl),
 - 4. 4-t-butyl,
 - 5. 4-toluyl,
 - 6. 4-(4-fluorophenyl)-,
 - 7. 4-(3-nitro-phenyl)-,
 - 8. 3-(3-nitro-phenyl)-,
 - 9. 4-quinolinyl,

- 5
10. Cl,
 11. OMe,
 12. Br,
 13. CF₃,
 14. cyclohexyl,
 15. butyl,
 16. (4-(2-tetrazol-5-yl)-phenyl)-,
 17. 4-(3-thiophenyl)- or
 18. 2-naphthyl-;
- 10
- b)
1. CONH-phenyl,
 2. CONH-4-biphenyl,
 3. CH₂-phenyl,
 4. CH₂-4-(biphenyl), or
 - 15 5. CH₂-4-(2'-carboxy-biphenyl).

17. A compound in accordance with Claim 14 as set forth
in the following table:

20



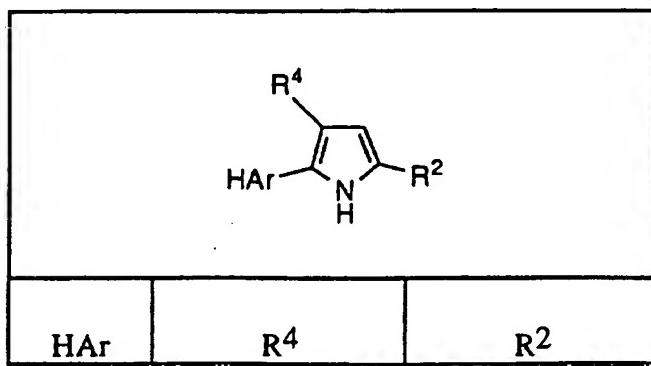
R ¹	R ²
H	Ph
H	4-(SMe)-Ph
H	4-(OPh)-Ph
H	4-(OEt)-Ph

- 147 -

H	4-(c-hex)-Ph
H	4-(CF ₃)-Ph
H	4-Br-Ph
H	4-(tBu)-Ph
H	4-Et-Ph
H	4-(SPh)-Ph
H	2-Me-Ph
H	4-(OMe)-Ph
H	4-Me-Ph
H	4-Cl-Ph
H	4-(OBu)-Ph
H	4-(OBn)-Ph
H	4-F-Ph
H	3,4-Cl-Ph
H	3-CF ₃ -Ph
H	3,4-F-Ph
H	3,4-(OCH ₂ O)-Ph
H	3-Cl-4-F-Ph
H	3-Me-4-Cl-Ph
H	4-OCF ₃ -Ph

18. A compound according to Claim 14, as set forth in the following table:

5



4-Pyr	4-CF ₃ -Ph	4-Cl-Ph
4-Pyr	3-Cl-Ph	4-Cl-Ph
3-Pyr	4-F-Ph	4-Cl-Ph
4-Pyr	4-OMe-Ph	4-Cl-Ph
4-Pyr	4-F-Ph	4-NO ₂ -Ph
4-Pyr	4-F-Ph	3-NO ₂ -Ph
4-Pyr	4-F-Ph	2-NO ₂ -Ph
4-Pyr	4-F-Ph	4-(COOEt)-Ph
4-Pyr	4-F-Ph	4-CN-Ph
4-Pyr	3-Br-Ph	4-Cl-Ph
4-Pyr	4-(1-Naphthyl)-Ph	4-Cl-Ph
4-Pyr	4-F-Ph	3-CN-Ph
4-Pyr	4-Br-Ph	4-Cl-Ph
4-Pyr	3-Br-Ph	4-Cl-Ph
4-Pyr	4-t-Bu-Ph	4-Cl-Ph

19. A compound according to Claim 14, as set forth in the following table:

5

wherein

R ⁴
3-Ph-Ph-
4-(4-MeO-Ph)-Ph-
3-(4-MeO-Ph)-Ph-
4-(4-CF ₃ -Ph)-Ph-

4-(1-naphthyl)-Ph-
4-(4-F-Ph)-Ph-
4-(3-NO ₂ -Ph)-Ph-
3-(3-NO ₂ -Ph)-Ph-
4-(4-Me-Ph)-Ph-
4-(2-thiophenyl)-Ph-
4-(3-thiophenyl)-Ph-
3-(2-thiophenyl)-Ph-
3-(3-thiophenyl)-Ph-

20. A compound according to Claim 14 as set forth in the following table:

 I				
R ¹	R ²	R ³	R ⁴	HAR-(R ^a) ₀₋₃
H	4-(COOH)-Ph	H	4-F-Ph	4-Pyr
H	4-Cl-Ph	H	4-tBu-Ph	4-Pyr
H	4-Cl-Ph	H	4-(3(i-Bu)-6-(A)Ph)Ph	4-Pyr
H	4-Cl-Ph	H	4-(4-(n-Bu)-Ph)-Ph	4-Pyr
H	4-Cl-Ph	H	4-(3-(iBu)-6-(B)-Ph)Ph	4-Pyr
H	4-Cl-Ph	H	4-(3-(iBu)-6-(C)Ph)Ph	4-Pyr
H	4-Cl-Ph	H	3-(4-(n-Bu)-Ph)-Ph	4-pyr
H	4-Cl-Ph	H	4-(3-(n-Pr)-6-(D)Ph)Ph	4-pyr
H	4-Cl-Ph	H	4-(5-(n-Bu)-thioPh)-Ph	4-Pyr
H	4-Cl-Ph	H	2-F-4-Br-phenyl	4-Pyr
H	4-Cl-Ph	H	2-(F)-4-(E)-Ph	4-Pyr
H	4-Cl-Ph	Br	4-F-Phenyl	4-Pyr
H	4-Cl-Ph	Cl	4-F-phenyl	4-Pyr
H	4-Cl-Ph	H	3,5-(Br)-phenyl	4-pyr
H	4-Cl-Ph	H	3,5-(2-thiophenyl)-Ph	4-pyr
H	4-Cl-Ph	H	CO ₂ Et	4-Pyr

- 150 -

H	4-Cl-Ph	H	COOH	4-Pyr
H	4-Cl-Ph	H	3,4-(4-OMe-Ph)-Ph	4-Pyr
H	4-Cl-Ph	H	3,5-(4-Me-Ph)-Ph	4-Pyr
H	4-Cl-Ph	H	3,5-(4-SMe-Ph)-Ph	4-Pyr
H	4-Cl-Ph	H	4-(NHCOMe)-Ph	4-Pyr
H	4-Cl-Ph	H	4-(OCH ₂ CO ₂ Me)-Ph	4-Pyr
H	4-Cl-Ph	H	4-(OMe)-Ph	4-Pyr
H	4-Cl-Ph	H	4-(iPr)-Ph	4-Pyr
H	4-Cl-Ph	H	4-(OBn)-Ph	4-Pyr
H	4-Cl-Ph	H	2-(OPr)-Ph	4-Pyr
H	4-Cl-Ph	H	CO-(4-(N-Ph)-Z)	4-Pyr
H	4-Cl-Ph	H	CONH-2-biphenyl	4-Pyr
H	4-Cl-Ph	H	3,5-(3-nitro-phenyl)-Ph	4-Pyr
H	4-Cl-Ph	H	4-(2-benzo-furanyl)-Ph	4-Pyr
H	4-Cl-Ph	H	3-Br-5-(2-thioPh)-Ph	4-Pyr
H	4-Cl-Ph	H	4-(G)-Ph	4-Pyr
H	4-Cl-Ph	H	4-(3,5-(CF ₃)-Ph)-Ph	4-Pyr
H	4-Cl-Ph	H	4-(2-(OMe)-Ph)-Ph	4-Pyr
H	4-Cl-Ph	H	4-(4-Cl-phenyl)-phenyl	4-Pyr
H	4-Cl-Ph	H	4-(CO ₂ Me)-phenyl	4-Pyr
H	4-Cl-Ph	H	2-F-4-(2-thioPh)-Ph	4-Pyr
H	4-Cl-Ph	H	4-(3-(NH ₂)-Ph)-Ph	4-Pyr
H	4-Cl-Ph	H	4-(3-(OMe)-Ph)-Ph	4-Pyr
H	4-Cl-Ph	H	2-Br-Ph	4-Pyr
H	4-Cl-Ph	H	2,6-F-Ph	4-Pyr
H	4-Cl-Ph	H	CONH-adamantyl	4-Pyr
H	4-Cl-Ph	H	CONHCH ₂ CH(Ph) ₂	4-Pyr
H	4-Cl-Ph	H	4-F-Ph	4-quinolinyl
H	4-Cl-Ph	H	CO ₂ Bn	4-Pyr
H	4-Cl-Ph	H	3-OBn-Ph	4-Pyr
H	4-Cl-Ph	H	4-(CHCH-Ph)-Ph	4-Pyr
H	4-Cl-Ph	H	9-phenanthrenyl	4-Pyr
H	4-Cl-Ph	H	3-(OPh)-Ph	4-Pyr
H	4-Cl-Ph	H	2-(OMe)-Ph	4-Pyr
H	2,4-Cl-Ph	H	4-F-Ph	4-Pyr
H	4-(N-CBz)-Z	H	4-F-Ph	4-Pyr
H	4-Ph-Ph	H	4-F-Ph	4-Pyr
H	4-Cl-phenyl	H	4-CN-phenyl	4-pyr
H	4-Cl-Ph	H	2,4-F-Phenyl	4-Pyr
H	4-Cl-phenyl	H	2,4,6-F-phenyl	4-Pyr
H	4-Cl-phenyl	H	2-(3-OMe-Ph)-Ph	4-Pyr
H	4-Cl-phenyl	H	2-(3-NO ₂ -Ph)-Ph	4-Pyr
H	4-Cl-phenyl	H	2-(thiophen-2-yl)-Ph	4-Pyr
H	4-Cl-phenyl	H	2-(OEt)-Ph	4-Pyr

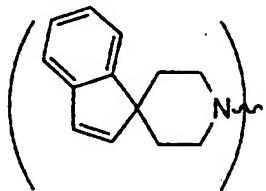
H	4-Cl-phenyl	H	2-(OH)-5-(Br)-Ph	4-pyr
H	4-Cl-phenyl	H	2-(OMe)-5-(Br)-Ph	4-pyr
H	4-Cl-phenyl	H	2,5-(OMe)-Ph	4-pyr
H	3-Cl-phenyl	H	4-F-Ph	4-pyr
H	4-F-phenyl	H	4-F-Ph	4-pyr
H	4-Cl-phenyl	H	4-(tetrazol-5-yl)-Ph	4-Pyr
H	4-F-Ph	H	4-(2-thiophenyl)-Ph	4-Pyr
H	2-F-phenyl	H	4-F-phenyl	4-Pyr
H	4-Cl-phenyl	H	2-F-4-(G)-Ph	4-Pyr
H	4-Cl-phenyl	H	4-(CONHtBu)-Ph	4-Pyr
H	2-(OMe)-4-(Cl)Ph	H	4-F-Ph	4-pyr
H	4-Cl-phenyl	H	4-F-Ph	4-(2,6-phenyl)-pyr
H	4-Cl-phenyl	H	4-F-Ph	4-(2-F)-pyr
H	4-Cl-phenyl	H	4-(J)Ph	4-pyr
H	4-Cl-phenyl	H	2-(Cl)-4-(Br)-Ph	4-pyr
H	4-Cl-phenyl	H	4-(CO ₂ Et)-Ph	4-pyr
H	4-N-(acetyl)-Z	H	4-F-Ph	4-Pyr
H	4-N-(Me)-Z	H	4-F-Ph	4-Pyr
H	4-N(OMe-CO)Z	H	4-F-Ph	4-pyr
H	4-N-(iPr-CO)Z	H	4-F-Ph	4-Pyr
H	4-piperidinyl	H	4-F-Ph	4-Pyr
H	4-Cl-phenyl	H	4-F-Ph	3-F-4-pyr
H	4-Cl-phenyl	H	4-F-Ph	3-(Me)-4-pyridyl
H	4-Cl-phenyl	H	2-(ethoxy)-5-(Br)-Ph	4-pyr
H	4-Cl-phenyl	H	2,5-(F)-Ph	4-pyr
H	4-Cl-Phenyl	H	2-(3-(Cl)-propoxy)-Ph	4-Pyr
H	4-Cl-phenyl	H	2-(propoxy)-5-(Br)-Ph	4-Pyr
H	4-Cl-Phenyl	H	2-(F)-5-(Br)-Ph	4-Pyr
H	4-Cl-Phenyl	H	4-(CON(Bn ₂))-Ph	4-pyr
H	4-Cl-phenyl	H	4-(3-Pyr)-Ph	4-Pyr
H	4-Cl-phenyl	H	4-(CO-(M))Ph	4-pyr
H	4-Cl-phenyl	H	4-(CONPn ₂)-Ph	4-pyr
H	4-Cl-phenyl	H	4-(CO-morpholinyl)-Ph	4-pyr
H	4-Cl-phenyl	H	4-(W)Ph	4-Pyr
H	4-Cl-phenyl	H	4-(Q)Ph	4-pyr
H	4-Cl-phenyl	H	4-(CO-spiroindene-1)-Ph	4-Pyr
H	4-Cl-phenyl	H	4-(CONMe ₂)-Ph	4-pyr
H	4-Cl-phenyl	H	4-(heterocycle-1)-Ph	4-pyr
H	4-Cl-phenyl	H	4-(heterocycle-2)-Ph	4-Pyr
H	4-Cl-phenyl	H	CO ₂ -(2-Ph-Ph)	4-pyr
H	4-Cl-phenyl	H	4-F-Ph	4-(2-methyl)pyridyl

- 152 -

H	4-Cl-phenyl	H	CHCHPh	4-pyr
H	4-Cl-phenyl	H	2-(CHCH-Ph)-Ph	4-pyr
H	4-Cl-phenyl	H	2-(OBn)-Ph	4-pyr
H	4-Cl-phenyl	H	2-(O-hexyl)-Ph	4-Pyr
H	4-Cl-phenyl	H	2-(O-nonyl)-Ph	4-pyr
H	4-Cl-phenyl	H	2-(O-iPr)-Ph	4-pyr
H	4-Cl-phenyl	H	2-(O-iBu)-Ph	4-pyr
H	4-Cl-phenyl	H	4-(2-pyr)-Ph	4-pyr
(X)	4-Cl-phenyl	H	2-F-4-Br-phenyl	4-pyr
H	4-Cl-phenyl	H	4-(Y)-2-F-Ph	4-pyr
H	4-Cl-phenyl	H	4-NO ₂ -Ph	4-pyr
H	c-hexyl	H	4-F-phenyl	4-pyr
H	N-(CBz)(Z)	H	CO ₂ Et	4-pyr
H	4-Cl-phenyl	H	4-NH ₂ -Ph	4-pyr
H	4-Cl-phenyl	H	4-(NHCO ₂ -butyl)-Ph	4-pyr

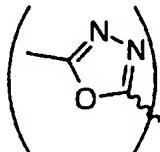
wherein: CO = carbonyl, Ph=phenyl, pyr=pyridyl, Pip=piperidinyl,
 OMe= methoxy, iPr=isopropyl, thioPh-thiophenyl, (A)=SO₂NH₂tBu,
 (B)=SO₂NH₂, (C)=SO₂NHCO₂nBu, (D)=tetrazol-5-yl, (E)=5-(n-Bu)-
 5 thiophen-2-yl, (G)=5-(Cl)-thiophen-2-yl, (J)=N-methyltetrazolyl,
 (M)=N-Boc-piperazin, (Q)=CO-spiroindane-1, (W)=CO-L-proline-
 OtBu, (X)=2-OH-Ph, (Y)=2-SO₂NH₂tBu-Ph, (Z)=piperidin-4-yl,

spiroindene-1 is:



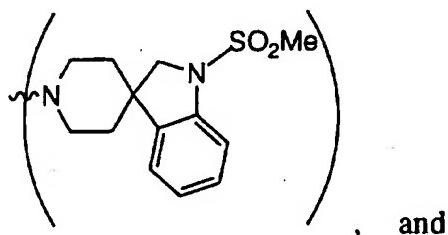
10

heterocycle-1 is:

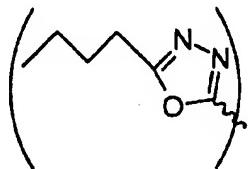


15 spiroindane-1 is:

- 153 -



heterocycle-2 is:



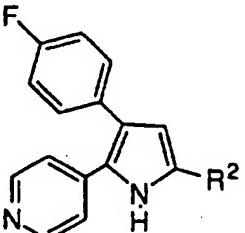
5

21. A compound according to Claim 1 which is:

- 3-(4-chlorophenyl)-5-(4-chlorophenyl)-2-(4-pyridyl)-pyrrole;
- 5-(4-chlorophenyl)-3-(4-fluorophenyl)-2-(4-pyridyl)-pyrrole;
- 5-(4-methylsulfinylphenyl)-3-(4-fluorophenyl)-2-(4-pyridyl)-pyrrole;
- 5-(4-methylaminophenyl)-3-(4-fluorophenyl)-2-(4-pyridyl)-pyrrole;
- 5-(4-aminophenyl)-3-(4-fluorophenyl)-2-(4-pyridyl)-pyrrole;
- 5-(3-aminophenyl)-3-(4-fluorophenyl)-2-(4-pyridyl)-pyrrole;
- 5-(2-aminophenyl)-3-(4-fluorophenyl)-2-(4-pyridyl)-pyrrole
- 5-(N-methyl-piperidin-4-yl)-3-(4-fluorophenyl)-2-(4-pyridyl)-pyrrole;
- 5-(4-chlorophenyl)-3-(biphenyl)-2-(4-pyridyl)-pyrrole;
- 3-(4-fluorophenyl)-5-(4-phenylsulfinylphenyl)-2-(4-pyridyl)pyrrole or
5-(N-methyl-piperidin-4-yl)-3-(4-fluorophenyl)-2-(4-pyridyl)pyrrole.

22. A compound in accordance with one of the following
20 tables:

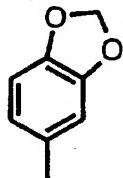
- 154 -



Example #	R ²
1	4-(MeS)-Ph
2	4-(PhO)-Ph
3	4-(EtO)-Ph
4	4-(c-hex)-Ph
5	4-(CF ₃)-Ph
6	4-Br-Ph
7	4-(t-Bu)-Ph
8	4-Et-Ph
9	4-(PhS)-Ph
10	2-Me-Ph
11	4-(MeO)-Ph
12	4-Me-Ph
13	4-Cl-Ph
14	4-(n-BuO)-Ph
15	4-(BzI O)-Ph
16	4-F-Ph
17	3,4-di-Cl-Ph
18	3-CF ₃ -Ph
19	3,4-di-F-Ph
20	3,4-(OCH ₂ O)-Ph
21	3-Cl-4-F-Ph
22	3-Me-4-Cl-Ph
23	4-CF ₃ O-Ph

- 155 -

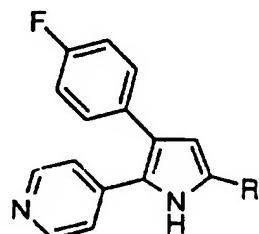
Me = methyl c-hex = cyclohexyl t-Bu = t-butyl Ph = phenyl Et = ethyl Bzl = benzyl Cbz = carboxybenzyl 3,4-(OCH₂O)-Ph represents



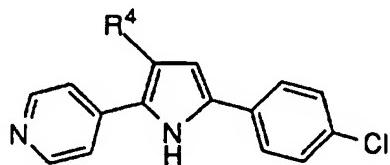
5

$ \begin{array}{c} R^4 \\ \\ \text{HAr} - \text{C} = \text{N} - \text{R}^2 \\ \\ \text{H} \end{array} $			
Ex. #	R ²	R ⁴	HAr
25	4-Cl-Ph	4-CF ₃ -Ph	4-Pyr
26	4-Cl-Ph	3-Cl-Ph	4-Pyr
27	4-Cl-Ph	4-F-Ph	3-Pyr
28	4-Cl-Ph	4-MeO-Ph	4-Pyr
29	4-NO ₂ -Ph	4-F-Ph	4-Pyr
30	3-NO ₂ -Ph	4-F-Ph	4-Pyr
31	2-NO ₂ -Ph	4-F-Ph	4-Pyr
32	4-(CO ₂ Et)- Ph	4-F-Ph	4-Pyr
33	4-CN-Ph	4-F-Ph	4-Pyr
34	4-Cl-Ph	3-Br-Ph	4-Pyr
35	4-Cl-Ph	4-(1- naphthyl)- Ph	4-Pyr
36	3-CN-Ph	4-F-Ph	4-Pyr
37	4-Cl-Ph	4-Br-Ph	4-Pyr
38	4-Cl-Ph	4-t-Bu-Ph	4-Pyr
39	4-Cl-Ph	2-F-4-Br- Ph	4-Pyr

- 156 -



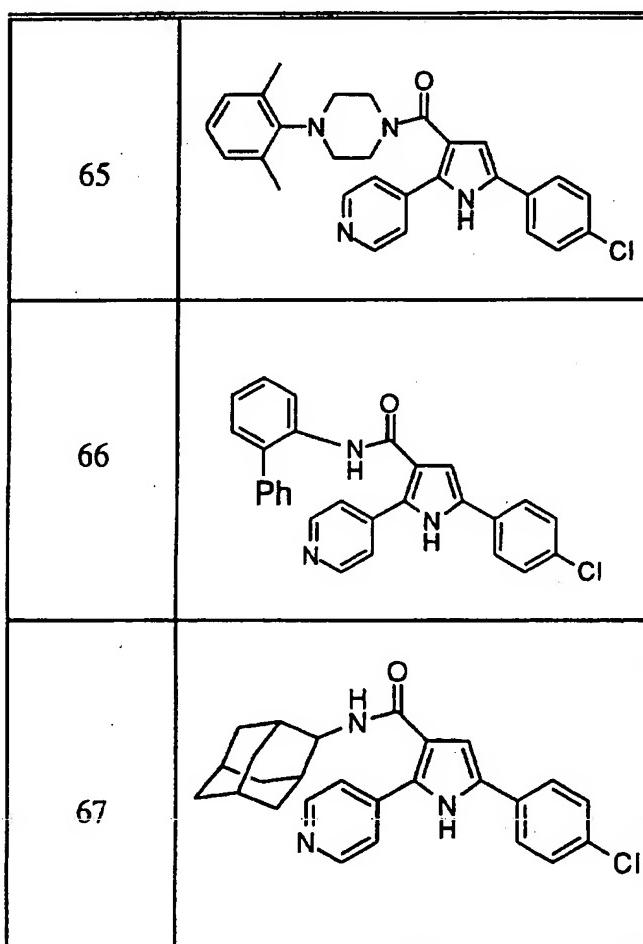
Example #	R
44	4-NH ₂ -Ph
45	3-NH ₂ -Ph
46	2-NH ₂ -Ph



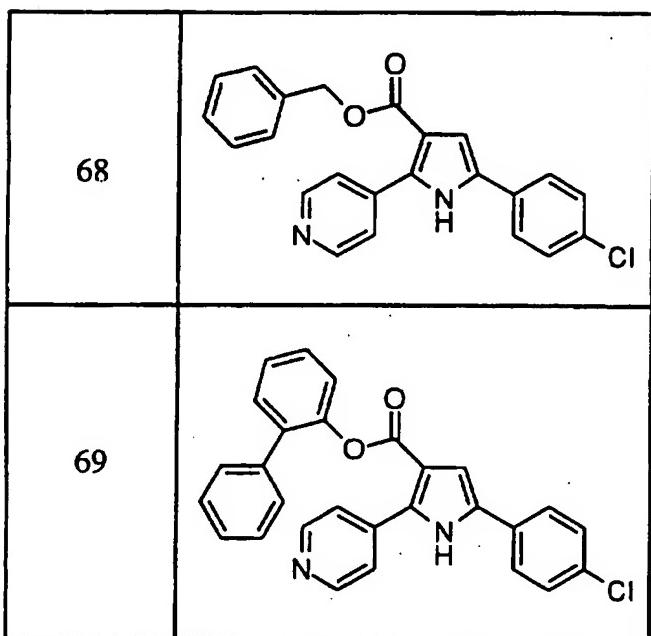
Example #	R ⁴
50	3-Ph-Ph-
51	4-(4-MeO-Ph)-Ph-
52	3-(4-MeO-Ph)-Ph-
53	4-(4-CF ₃ -Ph)-Ph-
54	4-(4-F-Ph)-Ph-
55	4-(3-NO ₂ -Ph)-Ph-
56	3-(3-NO ₂ -Ph)-Ph-

- 157 -

57	4-(4-Me-Ph)-Ph-
58	4-(2-thiophenyl)-Ph-
59	4-(3-thiophenyl)-Ph-
60	3-(2-thiophenyl)-Ph-
61	3-(3-thiophenyl)-Ph-



- 158 -



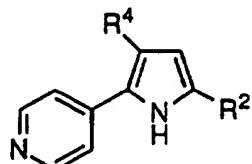
TABLE

R

Expl. No.	R
73	H
74	phenyl
75	n-butyl
76	4-methyl-phenyl

- 159 -

77	4-Cl-phenyl
78	2-pyridyl
79	4-F-phenyl
80	4-ethylphenyl
81	4-butylphenyl

TABLE

Expl. No.	R ²	R ⁴
82	4-(COOH)-Ph	4-F-Ph
83	4-Cl-Ph	4-(3-(i-Bu)-6-(SO ₂ NH-t-Bu)-phenyl)-Ph
84	4-Cl-Ph	4-(4-(n-Bu)-phenyl)-Ph
85	4-Cl-Ph	4-(3-(iBu)-6-(SO ₂ NH ₂)-phenyl)-Ph
86	4-Cl-Ph	3-(4-(n-Bu)-phenyl)-Ph
87	4-Cl-Ph	4-(5-(n-Bu)-thiophenyl)-Ph
88	4-Cl-Ph	2-(F)-4-(5-(n-Bu)-thiophen-2-yl)-Ph
89	4-Cl-Ph	3,5-di-Br-Ph
90	4-Cl-Ph	3,5-(thiophen-2-yl)-Ph
91	4-Cl-Ph	3,4-di-(4-OMe-Ph)-Ph

- 160 -

92	4-Cl-Ph	3,5-di-(4-Me- Ph)-Ph
93	4-Cl-Ph	4- (OCH ₂ CO ₂ Me)- Ph
94	4-Cl-Ph	4-OMe-Ph
95	4-Cl-Ph	4-i-Pr-Ph
96	4-Cl-Ph	4-OBzI-Ph
97	4-Cl-Ph	5-Ph-thiazol-2-yl
98	4-Cl-Ph	4-Br-thiophen-2- yl
99	4-Cl-Ph	2-OPr-Ph
100	4-Cl-Ph	3-thiophenyl
101	4-Cl-Ph	3,5-di-(3- nitrophenyl)-Ph
102	4-Cl-Ph	4-(benzofuran-2- yl)-phenyl
103	4-Cl-Ph	3-Br-5- (thiophen-2-yl)- Ph
104	4-Cl-Ph	4-(5-Cl- thiophen-2-yl)- Ph
105	4-Cl-Ph	4-(3,5-di-CF ₃ - Ph)-Ph
106	4-Cl-Ph	4-(2-OMe-Ph)- Ph
107	4-Cl-Ph	4-(4-Cl-Ph)-Ph
108	4-Cl-Ph	4-(CO ₂ Me)-Ph
109	4-Cl-Ph	2-F-4-(thiophen- 2-yl)-Ph
110	4-Cl-Ph	4-(3-(NH ₂)-Ph)- Ph
111	4-Cl-Ph	4-(3-(OMe)-Ph)- Ph
112	4-Cl-Ph	2-Br-Ph
113	4-Cl-Ph	2,6-di-F-Ph
114	4-Cl-Ph	3-OBnZl-Ph

115	4-Cl-Ph	4-(<i>trans</i> -ethenyl- Ph)-Ph
116	4-Cl-Ph	9-phenanthrenyl
117	4-Cl-Ph	3-(OPh)-Ph
118	4-Cl-Ph	2-(OMe)-Ph
119	2,4-di-Cl-Ph	4-F-Ph
120	t-Bu	4-F-Ph
121	Me	4-F-Ph
122	4-Cl-Ph	4-CN-Ph
123	4-Cl-Ph	2,4-di-F-Ph
124	4-Cl-Ph	2,4,6-tri-F-Ph
125	4-Cl-Ph	2-(3-OMe-Ph)- Ph
126	4-Cl-Ph	2-(3-NO ₂ -Ph)- Ph
127	4-Cl-Ph	2-thiophen-2-yl- Ph
128	4-Cl-Ph	2-indolyl
129	4-Cl-Ph	2-OEt-Ph
130	4-Cl-Ph	2-OH-5-Br-Ph
131	4-Cl-Ph	2-OMe-5-Br-Ph
132	4-Cl-Ph	5-(2-(CO ₂ Me)- thiophen-3-yl)- furan-2-yl
133	4-Cl-Ph	2,5-di-OMe-Ph
134	3-Cl-Ph	4-F-Ph
135	4-F-Ph	4-F-Ph
136	4-Cl-Ph	4-(tetrazol-5-yl)- Ph
137	4-F-Ph	4-(2-thiophenyl)- Ph
138	2-F-Ph	4-F-Ph
139	4-Cl-Ph	2-F-4-(2-(5-Cl- thiophen-2-yl)- Ph
140	4-Cl-Ph	4-(CONH-t-Bu)- Ph
141	2-OMe-4-Cl- Ph	4-F-Ph

142	4-Cl-Ph	4-(N-methyltetrazolyl)-Ph
143	4-Cl-Ph	2-Cl-4-Br-Ph
144	4-Cl-Ph	4-(CO ₂ E _t)-Ph
145	4-N-acetyl-piperidinyl	4-F-Ph
146	4-N-(methoxycarbonyl)-piperidinyl	4-F-Ph
147	4-N-(isopropoxycarbonyl)-piperidinyl	4-F-Ph
148	4-piperidinyl	4-F-Ph
149	4-Cl-Ph	2-ethoxy-5-Br-Ph
150	4-Cl-Ph	2,5-di-F-Ph
151	4-Cl-Ph	2-(3-Cl-propoxy)-Ph
152	4-Cl-Ph	2-propoxy-5-Br-Ph
153	4-Cl-Ph	2-F-5-Br-Ph
154	4-Cl-Ph	4-C(O)N(Bzl) ₂ -Ph
155	4-Cl-Ph	4-(3-Pyr)-Ph
156	4-Cl-Ph	4-C(O)-(N-Boc-piperazinyl))-Ph
157	4-Cl-Ph	4-(C(O)NPh ₂)-Ph
158	4-Cl-Ph	4-(C(O)-morpholinyl)-Ph
159	4-Cl-Ph	4-(C(O)-L-proline-O-(t-Bu))-Ph
160	4-Cl-Ph	4-C(O)-spiroindene)-phenyl

161	4-Cl-Ph	4-(5-Me-1,3,4-oxadiazol-2-yl)-Ph
162	4-Cl-Ph	4-(5-(n-Bu)-1,3,4-oxadiazol-2-yl)-Ph
163	4-Cl-Ph	<i>trans</i> -ethenyl-Ph
164	4-Cl-Ph	2-(t-CHCH-Ph)-Ph
165	4-Cl-Ph	2-(OBzl)-Ph
166	4-Cl-Ph	2-(O-(n-hexyl))-Ph
167	4-Cl-Ph	2-(O-(n-nonyl))-Ph
168	4-Cl-Ph	2-(O-iPr)-Ph
169	4-Cl-Ph	2-(O-iBu)-Ph
170	4-Cl-Ph	2-(O-(n-butyl))-Ph
171	4-Cl-Ph	2-(O-allyl)-Ph
172	4-Cl-Ph	2-(OCH ₂ -(2,6-di-Cl-Ph))-Ph
173	4-Cl-Ph	4-(2-pyr)-Ph
174	4-Cl-Ph	4-(2-(SO ₂ NH-(t-Bu))-Ph)-2-F-Ph
175	4-Cl-Ph	4-NO ₂ -Ph
176	c-hexyl	4-F-Ph
177	N-(CBzl)-piperidin-4-yl	CO ₂ Et
178	4-Cl-Ph	4-NH ₂ -Ph
179	4-Cl-Ph	4-(NHCO ₂ -(n-butyl))-Ph
180	4-Cl-Ph	4-(NHSO ₂ -(n-butyl))-Ph
181	4-Cl-Ph	4-(NHSO ₂ -thiophen-2-yl)-Ph
182	4-Cl-Ph	2-(OC(O)-propyl)-Ph

183	4-Cl-Ph	2-(O(CH ₂) ₃ SMe)-Ph
184	4-Cl-Ph	4-(NHCO ₂ Bzl)-Ph
185	4-Cl-Ph	4-(NHCO ₂ Ph)-Ph
186	N-(COOCH ₂ Ph-4-Cl)-piperidin-4-yl	4-F-Ph
187	N-(COOCH ₂ Ph-4-Br)-piperidin-4-yl	4-F-Ph
188	N-(COOCH ₂ Ph-4-Ph)-piperidin-4-yl	4-F-Ph
189	N-(COOCH ₂ Ph-4-NO ₂)-piperidin-4-yl	4-F-Ph
190	N-(COOCH ₂ Ph-3-Cl)-piperidin-4-yl	4-F-Ph
191	N-(COOCH ₂ Ph-2,4,5-tri-OMe)-piperidin-4-yl	4-F-Ph
192	N-(COOCH ₂ Ph-2-Cl)-piperidin-4-yl	4-F-Ph
193	4-NHCO ₂ Bzl-cyclohexyl	4-F-Ph

194	N-(COOCH ₂ Ph)-piperidin-3-yl	4-F-Ph
195	4-NH ₂ -cyclohexyl	4-F-Ph
196	piperidin-3-yl	4-F-Ph
197	4-Cl-Ph	2-OH-Ph
198	4-Cl-Ph	2-(4-Cl-SPh)-Ph
199	4-Cl-Ph	2-OPh-Ph
200	4-Cl-Ph	2-(O(CH ₂) ₃ OMe)-Ph
201	4-Cl-Ph	2-(OCONMe ₂)-Ph
202	4-Cl-Ph	2-(S-t-Bu)-Ph
203	4-Cl-Ph	4-(O(n-Pr))-Ph
204	4-Cl-Ph	2-(O(n-Pr))-4-(Br)-Ph
205	4-Cl-Ph	4-(5-((CH ₂) ₄ OH)-thiophen-2-yl)-Ph
206	4-Cl-Ph	4-(5-((CH ₂) ₄ azido)-thiophen-2-yl)-Ph
207	4-Cl-Ph	4-(3-OMe-Ph)-2-(O(n-Pr))-Ph
208	4-Cl-Ph	3-(O(n-Pr))-Ph
209	4-Cl-Ph	4-(3-NH ₂ -Ph)-2-(O(n-Pr))-Ph
210	4-Cl-Ph	benzyl
211	4-Cl-Ph	2-(furan-2-yl)-Ph
212	4-Cl-Ph	4-(furan-2-yl)-Ph
213	4-Cl-Ph	4-(2-OH-5-Br-Ph)-2-(O(n-Pr))-Ph

214	4-Cl-Ph	4-(5-((n-Bu))-thiophen-2-yl)-2-(O(n-Pr))-Ph
215	4-Cl-Ph	4-(3-(O(n-Bu))-Ph)-Ph
216	4-Cl-Ph	4-(5-((CH ₂) ₄ -amino)-thiophen-2-yl)-Ph
217	4-Cl-Ph	4-((n-Bu))-thiophen-2-yl)-Ph
218	4-Cl-Ph	1-naphthyl
219	4-Cl-Ph	quinolin-8-yl
220	4-Cl-Ph	4-(2-(OMe)-5-Br-Ph)-2-(O(n-Pr))-Ph
221	4-Cl-Ph	4-(cyclohexyl)-Ph
222	4-Cl-Ph	4-(n-Bu)-Ph
223	4-Cl-Ph	4-(5-(NO ₂)-thiophen-2-yl)-Ph
224	4-Cl-Ph	4-(3-(Me)-thiophen-2-yl)-Ph
225	4-Cl-Ph	4-(2,5-di-OMe-Ph)-Ph
226	4-Cl-Ph	4-(2,4,6-tri-Me-Ph)-Ph
227	4-Cl-Ph	4-(5-ethyl-thiophen-2-yl)-Ph
228	4-Cl-Ph	4-(5-Me-thiophen-2-yl)-Ph
229	4-Cl-Ph	4-(5-(n-Pr)-thiophen-2-yl)-Ph
230	4-Cl-Ph	4-(4-(n-Pr)-Ph)-Ph

231	4-Cl-Ph	4-I-Ph
232	4-Cl-Ph	4-(5-OMe-pyridin-2-yl)-Ph
233	4-Cl-Ph	4-(3-Me-Ph)-Ph
234	4-Cl-Ph	4-(3,4-(methylenedioxy)-Ph)-Ph
235	4-Cl-Ph	4-(3-(propoxy)-Ph)-Ph
236	4-Cl-Ph	4-(3-acetyl-Ph)-Ph
237	4-Cl-Ph	4-(3-NO ₂ -4-Me-Ph)-Ph
238	4-Cl-Ph	4-(3,4-di-OMe-Ph)-Ph
239	4-Cl-Ph	4-(3-(OCH ₂ CH ₂ OMe)-Ph)-Ph
240	4-Cl-Ph	4-(4-CN-3-Me-Ph)-Ph
241	4-Cl-Ph	4-(5-acetyl-thiophen-2-yl)-Ph
242	4-Cl-Ph	CH ₂ CH ₂ -Ph
243	4-Cl-Ph	CH ₂ CH(Me)-Ph
244	4-Cl-Ph	CH(Me)CH ₂ -(3,4-(methylenedioxy)-Ph)
245	4-Cl-Ph	4-(3-(OCH ₂ CH ₂ OEt)-Ph)-Ph
246	4-Cl-Ph	4-(indan-1-on-5-yl)-Ph
247	4-Cl-Ph	4-(4-Et-Ph)-Ph
248	4-Cl-Ph	4-(5-CO ₂ Etfuran-2-yl)-Ph
249	4-Cl-Ph	4-(2-ethyl-phenyl)-Ph

- 168 -

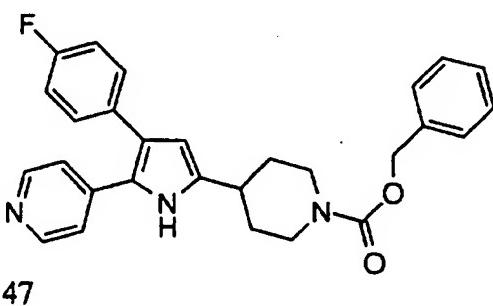
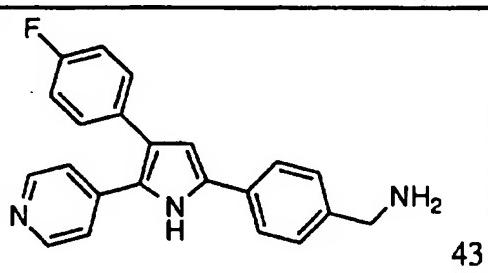
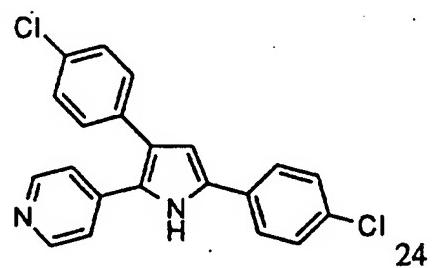
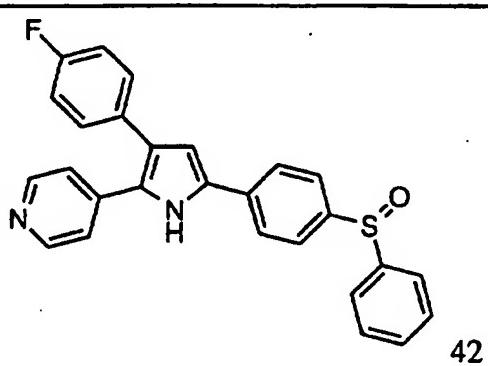
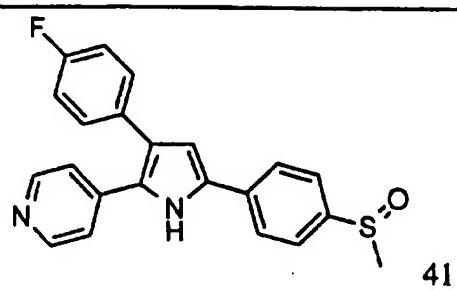
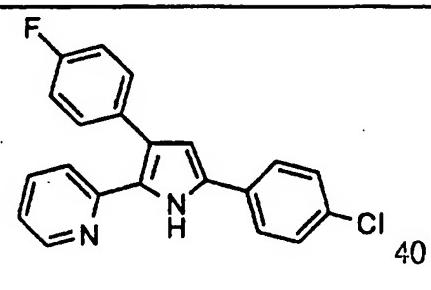
250	4-Cl-Ph	2,4-di-propoxy- Ph
251	4-Cl-Ph	2-propoxy-5-F- Ph
252	4-Cl-Ph	3,5-di-Br-2- propoxy-Ph
253	4-Cl-Ph	2-propoxy-5-Cl- Ph
254	4-Cl-Ph	2-propoxy-3-Cl- Ph
255	4-Cl-Ph	2-propoxy-3-F- Ph
256	4-Cl-Ph	4-(5- pyrimidinyl)-Ph
257	4-Cl-Ph	cyclohexyl
258	2-Br-Ph	4-F-Ph

Ex.	R ¹	(R ^a) _{o-3} -Har	R ⁴	R ³	R ²
259	H	3-Pyr	4-F-Ph	H	4-Cl- Phenyl
260	H	4-Pyr	4-F-Ph	Br	4-Cl- Phenyl
261	H	4-Pyr	4-F-Ph	Cl	4-Cl-Ph
262	H	4-quinolinyl	4-F-Ph	H	4-Cl-Ph
263	H	4-(2-F)-pyr	4-F-Ph	H	4-Cl-Ph
264	H	3-F-4-pyr	4-F-Ph	H	4-Cl-Ph
265	H	3-(Me)- 4-pyridyl	4-F-Ph	H	4-Cl-Ph

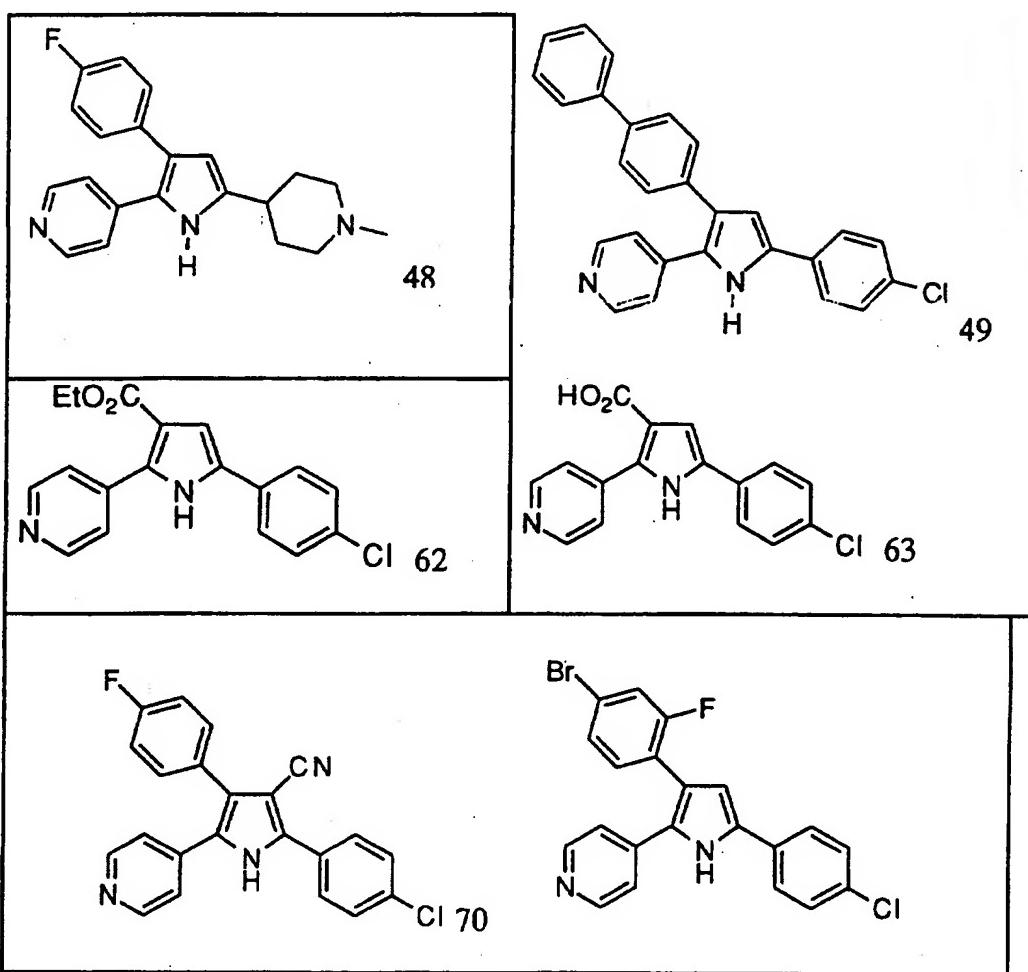
- 169 -

266	H	4-(2-Me)-pyridyl	4-F-Ph	H	4-Cl-Ph
267	2-OH-Ph	4-pyr	2-F-4-Br-Ph	H	4-Cl-Ph
268	H	4-pyr	4-F-Ph	Me	4-Cl-Ph
269	H	4-Pyr	4-F-Ph	Et	4-Cl-Ph
270	H	4-Pyr	4-F-Ph	Ph	4-Cl-Ph
271	H	2-NH ₂ -pyridin-4-yl	4-F-Ph	H	4-Cl-Ph
272	H	pyrimidin-4-yl	4-F-Ph	H	4-Cl-Ph
273	H	quinolin-6-yl	4-F-Ph	H	4-Cl-Ph
274	H	2-F-pyridin-5-yl	4-F-Ph	H	4-Cl-Ph
275	H	4-Pyr	3-CF ₃ -Ph	Me	N-methyl-piperidin-4-yl
276	H	4-Pyr	3-CF ₃ -Ph	Me	piperidin-4-yl
277	H	2-OH-pyridin-5-yl	4-F-Ph	H	4-Cl-Ph
278	H	pyridazin-4-yl	4-F-Ph	H	4-Cl-Ph
279	H	4-Pyr	4-F-Ph	H	2-CN-Ph
280	H	4-Pyr	2-CN-Ph	H	4-Cl-Ph
281	H	4-Pyr	4-F-Ph	n-Bu	4-Cl-Ph
282	H	4-Pyr	2-propoxy-4-(2-Ph ethynyl)-Ph	H	4-Cl-Ph
283	H	4-Pyr	4-(2-propenyl)-cyclohexen-1-yl	H	4-Cl-Ph
284	H	4-Pyr	N-(Cbz)-piperidin-4-yl	H	4-Cl-Ph
285	H	4-Pyr	i-Propyl	H	4-Cl-Ph

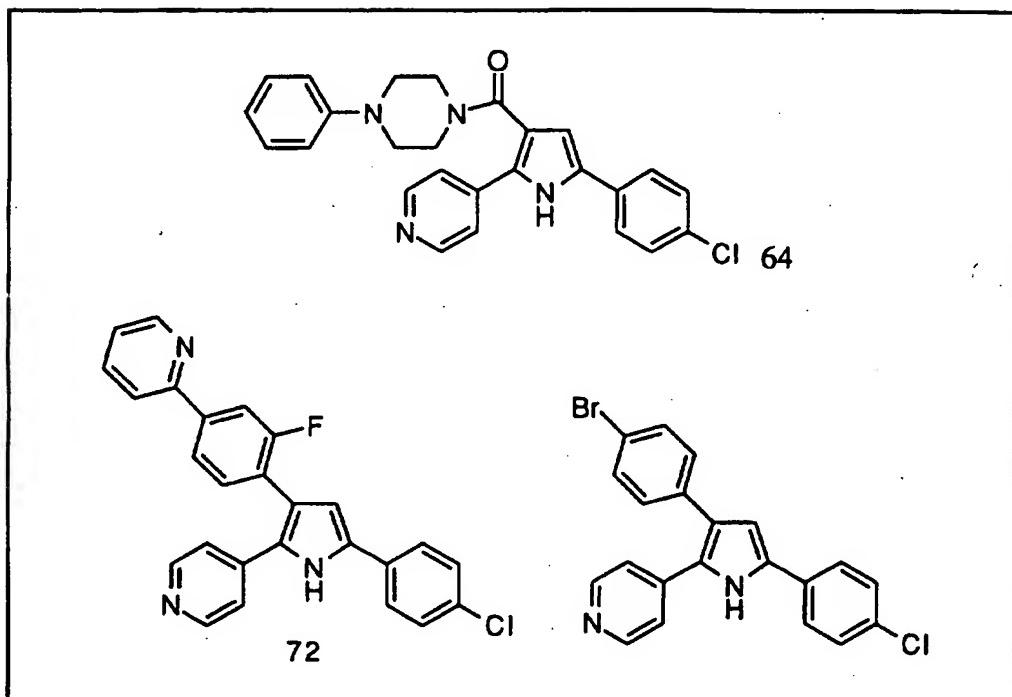
- 170 -



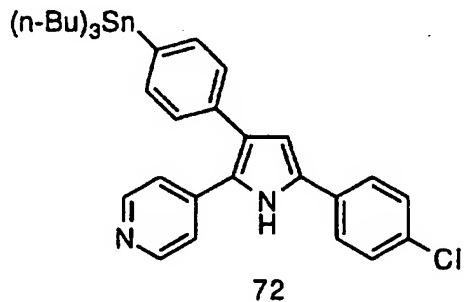
- 171 -



- 172 -



23. A compound represented by the formula:



5

24. A method of treating diabetes disease in a mammal in need of such treatment, which comprises administering to said mammal an effective amount of a glucagon antagonist.

10

25. A method of treating diabetes disease in a mammal in need of such treatment, which comprises administering to said mammal an effective amount of a glucagon antagonist of claim 1.

5 26. A method of treating a cytokine mediated disease in a mammal in need of such treatment, which comprises administering to said mammal a compound of claim 1 an amount effective for treating said cytokine mediated disease.

10 27. The method according to claim 26 wherein the cytokine inhibited is IL-1.

28. The method according to claim 26 wherein the cytokine inhibited is TNF.

15 29. The method according to claim 26 wherein the cytokine inhibited is IL-8.

20 30. The method according to claim 26 wherein the cytokine mediated disease is septic shock, endotoxic shock, gram negative sepsis or toxic shock syndrome.

25 31. The method according to claim 26 wherein the cytokine mediated disease is bone resorption disease, graft versus host reaction, atherosclerosis, arthritis, osteoarthritis, rheumatoid arthritis, gout, psoriasis, or a topical inflammatory disease.

30 32. The method according to claim 26 wherein the cytokine mediated disease is adult respiratory distress syndrome, asthma, or chronic pulmonary inflammatory disease.

33. The method according to claim 26 wherein the cytokine mediated disease is cardiac and renal reperfusion injury, thrombosis or glomerulonephritis.

34. The method according to claim 26 wherein the cytokine mediated disease is Crohn's disease, ulcerative colitis or inflammatory bowel disease.

5

35. The method according to claim 26 wherein the cytokine mediated disease is cachexia.

10 36. The method according to claim 26 wherein the cytokine mediated disease is a viral infection.

15 37. A method of treating inflammation mediated by excess production of prostaglandin's in a human in need of such treatment, which comprises administering to said human an effective cytokine interfering amount of a compound of claim 1.

38. The method of claim 31 wherein the prostaglandin is PGE2.

20 39. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/18539

A. CLASSIFICATION OF SUBJECT MATTER		
IPC(6) :C07D 401/04; A61K 31/44 US CL :546/276.4; 514/343 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) U.S. : 546/276.4; 514/343		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ONLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,267,185 A (FINIZIO) 12 May 1981 (12/05/81), see entire document, especially column 2.	1-39 (parts)
A	US 4,652,582 A (WILKERSON) 24 March 1987 (24/03/87), see entire document, especially column 2.	1-39 (parts)
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "T" later documents published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document published on or after the international filing date "L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 13 JANUARY 1997	Date of mailing of the international search report 14 FEB 1997	
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks, Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer <i>U. J. H. T. J. A. / EJ</i> R.W. RAMSUEB aco Telephone No. (703) 308-1235	

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US96/18539**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 1-39 (parts) because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/18539

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE**2. Where no meaningful search could be carried out, specifically:**

The multitude of variables and their permutations and combinations (e.g. HAr, Ra, Rb, R1, R2, R3, R4, R20 etc.) result in claimed subject matter that is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Note also that the claimed subject matter lacks a significant structural element qualifying as the special technical feature that clearly defines a contribution over the art. The subject matter claimed contains a pyrrole ring which does not define a contribution over the prior art. Therefore, the first discernable invention as found in Example 1, (the compound therein, a pharmaceutical composition therewith and a method of treating diabetes therewith) has been searched.